

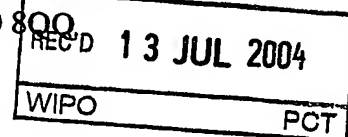


PCT/GB 2004 / 0 0 2 6 8 0



INVESTOR IN PEOPLE

The Patent Office
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Newport
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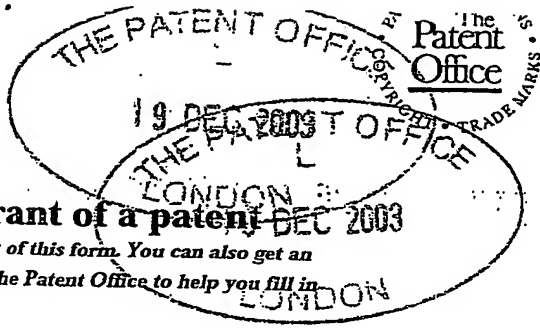
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Request for grant of a patent

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The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference PA 531

2. Patent application number
(The Patent Office will fill in this part)

0329471.7

3. Full name, address and postcode of the or of each applicant (underline all surnames)

CELLTECH R&D LIMITED
208 BATH ROAD
SLOUGH, BERKSHIRE
SL1 3WE
UNITED KINGDOM

Patents ADP number (if you know it)

8121485001

If the applicant is a corporate body, give the country/state of its incorporation

ENGLAND AND WALES

4. Title of the invention

PROCESS

5. Name of your agent (if you have one)

THOMPSON, JOHN

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

CELLTECH R&D LIMITED
208 BATH ROAD
SLOUGH, BERKSHIRE
SL1 2WE
UNITED KINGDOM

Patents ADP number (if you know it)

8121485001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

YES

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an applicant, or
 - c) any named applicant is a corporate body.
- See note (d))

Patents Form 1/77

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Continuation sheets of this form

Description 45

Claim(s) 5

Abstract 0

Drawing(s) 0

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature

J. Thompson

Date 18-December-03

12. Name and daytime telephone number of person to contact in the United Kingdom DR JOHN THOMPSON 01753 442193

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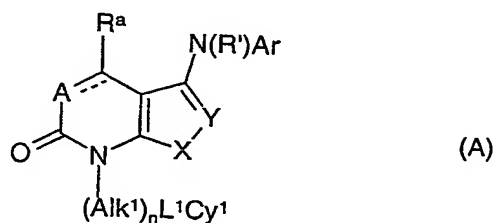
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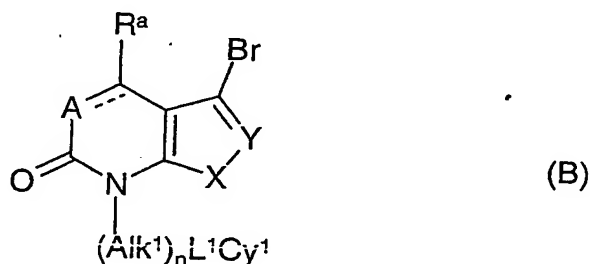
The present invention relates to 3-aminothienopyridone derivatives, to processes for their preparation and to their use as intermediates in the manufacture of inhibitors of p38 kinase.

In co-pending PCT application number PCT/GB03/02667 (based on UK patent application GB 0214268.5) we describe a series of bicyclic heterocycle derivatives of formula (A):



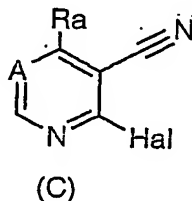
The compounds are potent and selective inhibitors of p38 kinases and are of use in the treatment of autoimmune, inflammatory and other diseases.

In co-pending PCT application number PCT/GB03/02667 the compounds of formula (A) are generally prepared by reaction of a bromide of formula (B):

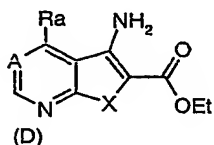


with an amine ArNH_2 , in the presence of a palladium catalyst, a phosphine ligand and a base.

The bromide (B) is generally prepared in a multi-step process from a cyanopyridine or cyanopyrimidine of formula (C):

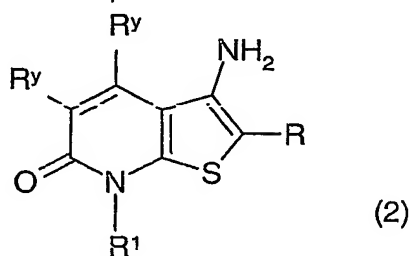


For example, compounds of formula (B) wherein A is a $-C(R^b)=$ group, X is a $-O-$ or $-S-$ atom or $-NH-$ group and Y is a substituted carbon atom in which the substituent is an esterified carboxyl group, for example a $-CO_2Alk^2$ group, may be prepared in several steps, starting by reacting a compound of
 5 formula (C) with a reagent of formula $HXCH_2CO_2Et$ (where Et is an ethyl group and X is a $-O-$ or $-S-$ atom or $-NH-$ group) to give an amine of formula (D):



The resulting amine of formula (D) may be converted to a bromide by
 10 reaction with an alkyl nitrite and a copper salt e.g. copper (II) bromide. The resulting bromide may then be oxidised to give a pyridine-N-oxide, which then undergoes rearrangement to give a pyridone, which is then finally N-alkylated or N-arylated to yield a desired bromide of formula (B).

Although the process to the bromides of formula (B) in PCT application
 15 number PCT/GB03/02667 is suitable for preparing compounds of formula (A) in acceptable yields, we have now found an improved process for preparing certain halides, such as bromides, comprising the use of an intermediate of formula (2). Thus in one aspect of the invention we provide a compound of formula (2):



20 wherein:

R is a $-CN$, $-NO_2$, $-CO_2Alk^2$, $-COC_{1-6}alkyl$ or $-CONHet^2$ group;

Alk^2 is an optionally substituted alkyl, arylalkyl-, aryl, aryloxyalkyl-, alkanoyloxyalkyl or aroyloxyalkyl- group;

25 $NHet^2$ is an optionally substituted 4 to 6 membered heterocycloalkyl group attached through a nitrogen atom to the group $-CO$;

R^1 is an optionally substituted aryl, heteroaryl, cycloalkyl or heterocycloalkyl group;

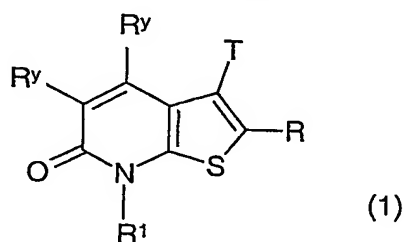
R^y , which may be the same or different, is each a hydrogen atom or a hydrogen atom precursor;

- 5 and the salts, solvates, hydrates, protected derivatives and N-oxides thereof; for use in the manufacture of halides of formula (1), as defined below.

The intermediate amines of formula (2) are novel compounds and form a further aspect of the invention.

- 10 The amines of formula (2) are versatile and useful compounds. In particular they are of use in the preparation of halides e.g. bromides of formula (1) or amines of formula (1A) as described below. The processes are simple, versatile, short and easy to operate and are particularly amenable to the large scale synthesis of the desired compounds.

- 15 Thus according to another aspect of the invention we provide a process for the manufacture of a halide of formula (1):

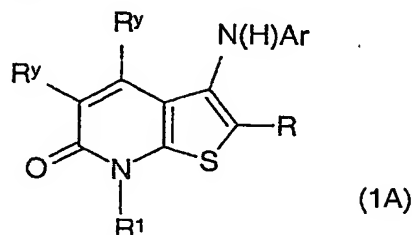


wherein R, R^1 , R^y are as defined for formula (2) and T is a halogen atom; which comprises diazotization of an intermediate amine of formula (2), followed by halide displacement.

- 20 The process according to this aspect of the invention may be performed in the presence of a diazotization reagent e.g. a nitrite such as an alkyl nitrite, for example t-butyl nitrite or a metal nitrite such as an alkali metal nitrite e.g. sodium nitrite in the presence of an inorganic acid such as sulphuric acid or hydrochloric acid, followed by addition of a source of halide
25 such as a copper salt, for example copper (II) bromide, copper (II) chloride or copper (II) iodide in the presence of a solvent, for example a nitrile such as acetonitrile at a temperature from about 0° to around 65°C.

- 30 In addition to their use in the process described above compounds of formula (2) may also be used for other purposes such as for the direct preparation of certain compounds of formula (1A). The invention extends to

such other uses and in particular we provide a process for the preparation of compounds of formula (1A):



wherein R, R¹, R^y are as defined for formula (2) and Ar is an optionally substituted aromatic or heteroaromatic group;

which comprises reacting a compound of formula (2) as described above, with a compound ArQ, wherein Q is a leaving group, in the presence of a transition metal catalyst e.g. a palladium catalyst. The reaction may be conveniently carried out in a solvent such as toluene or ethylene glycol dimethylether at an elevated temperature, e.g. the reflux temperature, using a catalyst such as tris(dibenzylideneacetone)dipalladium(0), a phosphine ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or tri-*tert*-butylphosphine and a base such as caesium carbonate or tripotassium phosphate. Alternatively, the reaction may be carried out in the presence of a copper catalyst, e.g. copper(I) iodide, optionally in a suitable solvent such as an alcohol, e.g. isopropanol, or an ether, e.g. 1,4-dioxane, in the presence of a base, e.g. tripotassium phosphate. A chelating ligand such as ethylene glycol or *N,N*-dimethylethanolamine may also be used.

The novel intermediates of formula (2) may be prepared by a number of processes, as described hereinafter, and these form further aspects of the invention.

In the compounds of formulae (1), (1A) and (2) and where appropriate in the other formulae described herein the various terms used to define each substituent are to be understood to have the meanings as defined hereinafter, unless otherwise stated.

It will be appreciated that compounds of formulae (1), (1A) and (2) may have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof in any proportion, including racemates. Formulae (1), (1A) and (2) and the formulae hereinafter are intended to

represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formulae (1), (1A) and (2) may exist as tautomers, for example keto ($\text{CH}_2\text{C}=\text{O}$)-enol ($\text{CH}=\text{CHOH}$) tautomers. Formulae (1), (1A) and (2) and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

It will be further appreciated by one skilled in the art that the term "protected derivatives" is intended to mean that the relevant compound will include any group which may be readily removed from a compound of formulae (1), (1A) and (2). Conventional protecting groups may be used in accordance with standard practice [see, for example, Greene, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1999]. Examples include amine protecting groups, such as carbamates, for example *tert*-butyl carbamate (BOC) or benzyl carbamate (Cbz), or alcohol protecting groups for example esters such as methyl or ethyl ester or benzyl ethers, for example, *para*-methoxybenzyl ether or benzyl ether or ethers such as tetrahydropyran-2-yl ether or alkyl ethers e.g. methoxy.

It will also be appreciated that the term "hydrogen atom precursor" is intended to include any atoms or groups which may be readily removed from a compound of formulae (1), (1A) and (2), or any subsequent compound, in order to give a hydrogen atom. Suitable examples include halogen atoms such as chlorine, bromine or iodine or $-\text{CO}_2\text{H}$, esters, e.g. $-\text{CO}_2\text{Alk}^2$ or $-\text{CN}$ groups.

Examples of leaving groups represented by the group Q include halogen atoms, e.g. a bromine, iodine or chlorine atom or sulfonyloxy groups such as an alkylsulfonyloxy, e.g. trifluoromethylsulfonyloxy or arylsulfonyloxy, e.g. *p*-toluenesulfonyloxy groups. Particular examples include halogen atoms especially bromine or iodine.

Thus as used herein the term "alkyl" whether present as a group or part of a group includes straight or branched C_{1-6} alkyl groups, for example C_{1-4} alkyl groups such as methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *s*-butyl, *i*-butyl or *t*-butyl groups. Optional substituents when present on these groups include those optional substituents mentioned hereinafter.

The term "alkylene chain" is intended to include the alkyl groups as just described in which a terminal hydrogen atom is replaced by a covalent bond to give a divalent chain. Examples include optionally substituted C₁₋₆ alkylene chains such as -CH₂-, -CH₂CH₂-, -CH(CH₃)CH₂-, -(CH₂)₂CH₂-, -(CH₂)₃CH₂-,
 5 -CH(CH₃)(CH₂)₂CH₂-, -CH₂CH(CH₃)CH₂-, -C(CH₃)₂-, -C(CH₃)₂CH₂-,
 -CH₂C(CH₃)₂CH₂-, -(CH₂)₂CH(CH₃)CH₂-, -CH(CH₃)CH₂CH₂-,
 -CH(CH₃)CH₂CH(CH₃)CH₂-, -CH₂CH(CH₃)CH₂CH₂-, -(CH₂)₂C(CH₃)₂CH₂-,
 -(CH₂)₄CH₂- or -(CH₂)₅CH₂-. Optional substituents when present on these chains include those optional substituents mentioned hereinafter.

10 The term halogen is intended to include fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" is intended to include those alkyl groups just mentioned substituted by one, two or three of the halogen atoms just described. Particular examples of such groups include -CF₃, -CCl₃, -CHF₂, -
 15 CHCl₂, -CH₂F and -CH₂Cl groups.

The term "alkoxy" as used herein is intended to include straight or branched C₁₋₆alkoxy e.g. C₁₋₄alkoxy such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, i-butoxy and t-butoxy. "Haloalkoxy" as used herein includes any of these alkoxy groups substituted by one, two or three
 20 halogen atoms as described above. Particular examples include -OCF₃, -OCCl₃, -OCHF₂, -OCHCl₂, -OCH₂F and -OCH₂Cl groups.

As used herein the term "alkylthio" is intended to include straight or branched C₁₋₆alkylthio, e.g. C₁₋₄alkylthio such as methylthio or ethylthio.

The optional substituents which may be present on alkyl groups or
 25 alkylene chains include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or -OH, -CO₂H, -CO₂R⁴ [where R⁴ is an optionally substituted straight or branched C₁₋₆alkyl group], e.g. -CO₂CH₃ or -CO₂C(CH₃)₃, -CONHR⁴, e.g. -CONHCH₃, -CON(R⁴)₂, e.g. -
 30 CON(CH₃)₂, -COR⁴, e.g. -COCH₃, C₁₋₆alkoxy, e.g. methoxy or ethoxy, haloC₁₋₆alkoxy, e.g. trifluoromethoxy or difluoromethoxy, thiol (-SH), -S(O)R⁴, e.g. -S(O)CH₃, -S(O)₂R⁴, e.g. -S(O)₂CH₃, C₁₋₆alkylthio e.g. methylthio or ethylthio, amino, -NHR⁴, e.g. -NHCH₃ or -N(R⁴)₂, e.g. -N(CH₃)₂ groups. Where two R⁴

groups are present in any of the above substituents these may be the same or different.

In addition when two R^4 alkyl groups are present in any of the optional substituents just described these groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom or heteroatom containing group selected from $-O-$, $-S-$, $-N(R^4)-$, $-C(O)-$ or $-C(S)-$ groups. Particular examples of such heterocyclic rings include piperidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

In general in the compounds of formulae (1), (1A) and (2) the term "cycloalkyl group" includes optionally substituted non-aromatic cyclic or multicyclic, saturated C_{3-10} ring systems, such as, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. Particular examples include optionally substituted C_{3-6} cycloalkyl ring systems such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Optional substituents present on these groups include those substituents mentioned hereinafter.

The term "heterocycloalkyl group" refers to an optionally substituted non-aromatic 3 to 10 membered saturated monocyclic or multicyclic hydrocarbon ring system containing one, two, three or four heteroatoms or heteroatom-containing linker groups L^1 as defined hereinafter. Particular examples include 3 to 6 membered monocyclic ring systems containing one or two heteroatoms. Optional substituents present on the heterocycloalkyl groups include those substituents mentioned hereinafter.

When L^1 is present in heterocycloalkyl groups as a linker atom or group it may be any divalent linking atom or group. Particular examples include $-O-$ or $-S-$ atoms or $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-C(S)-$, $-S(O)-$, $-S(O)_2-$, $-N(R^5)-$ [where R^5 is a hydrogen atom or a straight or branched alkyl group], $-N(R^5)O-$, $-N(R^5)N-$, $-CON(R^5)-$, $-OC(O)N(R^5)-$, $-CSN(R^5)-$, $-N(R^5)CO-$, $-N(R^5)C(O)O-$, $-N(R^5)CS-$, $-S(O)_2N(R^5)-$, $-N(R^5)S(O)_2-$, $-N(R^5)CON(R^5)-$, $-N(R^5)CSN(R^5)-$ or $-N(R^5)SO_2N(R^5)-$ groups. Where L^1 contains two R^5 groups these may be the same or different.

Particular examples of heterocycloalkyl groups include optionally substituted tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl,

pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolidinyl, pyrazolidinyl, tetrahydropyrimidinyl, thiazolidinyl, piperidinyl, homopiperidinyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, homopiperazinyl, dihydroisothiazolyl, dihydroisothiazole 1,1-dioxide, e.g. 2,3-dihydroisothiazole 1,1-dioxide, or tetrahydropyrazinyl groups.

The optional substituents which may be present on the cycloalkyl or heterocycloalkyl groups include one, two, three or more substituents selected from halogen atoms, or C₁₋₆alkyl, e.g. methyl or ethyl, haloC₁₋₆alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. -C(OH)(CF₃)₂, C₁₋₆alkoxy, e.g. methoxy or ethoxy, haloC₁₋₆alkoxy, eg. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C₁₋₆alkylthiol, e.g. methylthiol or ethylthiol, carbonyl (=O), thiocarbonyl (=S), imino (=NR^{4a}) [where R^{4a} is an -OH group or a C₁₋₆alkyl group], or -(Alk³)_vR⁶ groups in which Alk³ is a straight or branched C₁₋₃alkylene chain, v is zero or the integer 1 and R⁶ is a C₃₋₈cycloalkyl, -OH, -SH, -N(R⁷)(R⁸) [in which R⁷ and R⁸ is each independently selected from a hydrogen atom or an optionally substituted alkyl or C₃₋₈cycloalkyl group], -OR⁷, -SR⁷, -CN, -NO₂, -CO₂R⁷, -SOR⁷, -SO₂R⁷, -SO₃R⁷, -OCO₂R⁷, -C(O)R⁷, -OC(O)R⁷, -C(S)R⁷, -C(O)N(R⁷)(R⁸), -OC(O)N(R⁷)(R⁸), -N(R⁷)C(O)R⁸, -C(S)N(R⁷)(R⁸), -N(R⁷)C(S)R⁸, -SO₂N(R⁷)(R⁸), -N(R⁷)SO₂R⁸, -N(R⁷)C(O)N(R⁸)(R⁹) [where R⁹ is as defined for R⁷], -N(R⁷)C(S)N(R⁸)(R⁹), -N(R⁷)SO₂N(R⁸)(R⁹) or an optionally substituted aromatic or heteroaromatic group.

Examples of -NHet² groups are defined hereinafter.

Particular examples of Alk³ chains include -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂- and -CH(CH₃)CH₂- chains.

When R⁶, R⁷, R⁸ and/or R⁹ is present as a C₃₋₈cycloalkyl group it may be for example a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group. Optional substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, or hydroxy or C₁₋₆alkoxy, e.g. methoxy, ethoxy or *i*-propoxy groups.

When the groups R^7 and R^8 or R^8 and R^9 are both alkyl groups these groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom or heteroatom containing group selected from $-O-$, $-S-$, $-N(R^8)-$, $-C(O)-$ or $-C(S)-$ groups. Particular examples of such heterocyclic rings include piperidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When R^6 is an optionally substituted aromatic or heteroaromatic group it may be any such group as described hereinafter.

The terms "aromatic group" and "aryl group" are intended to include for example optionally substituted monocyclic ring C_{6-12} aromatic groups, such as phenyl, or bicyclic fused ring C_{6-12} aromatic groups, such as, 1- or 2-naphthyl groups.

The terms "heteroaromatic group" and "heteroaryl group" are intended to include for example optionally substituted C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms (or oxidised versions thereof). In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Each of these aromatic or heteroaromatic groups may be optionally substituted by one, two, three or more R^{10} atoms or groups as defined below.

Particular examples of monocyclic ring heteroaromatic groups of this type include pyrrolyl, furyl, thienyl, imidazolyl, N- C_{1-6} alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl, or triazinyl.

Particular examples of bicyclic ring heteroaromatic groups of this type include benzofuryl, benzothienyl, benzotriazolyl, indolyl, indazolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl,

benzisoaxazolyl, benzopyranyl, quinazoliny, quinoxaliny, naphthyridiny, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]-pyridyl, quinoliny, isoquinoliny or phthalaziny.

Optional substituents which may be present on aromatic or heteroaromatic groups include one, two, three or more substituents, each selected from an atom or group R^{10} in which R^{10} is R^{10a} or $-L^2Alk^5(R^{10a})_r$, where R^{10a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, hydroxyl ($-OH$), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol ($-SH$), substituted thiol, $-COR^{11}$ [where R^{11} is an $-L^6Alk^3(R^{10a})_r$, aryl or heteroaryl group], $-CSR^{11}$, $-SO_3H$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_3R^{11}$, $-SO_2NH_2$, $-SO_2NHR^{11}$, $-SO_2N(R^{11})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{11}$, $-CSNHR^{11}$, $-CON(R^{11})_2$, $-CSN(R^{11})_2$, $-N(R^{12})SO_2R^{11}$ [where R^{12} is a hydrogen atom or a straight or branched alkyl group], $-N(SO_2R^{11})_2$, $-N(R^{12})SO_2NH_2$, $-N(R^{12})SO_2NHR^{11}$, $-N(R^{12})SO_2N(R^{11})_2$, $-N(R^{12})COR^{11}$, $-N(R^{12})CONH_2$, $-N(R^{12})CONHR^{11}$, $-N(R^{12})CON(R^{11})_2$, $-N(R^{12})CSNH_2$, $-N(R^{12})CSNHR^{11}$, $-N(R^{12})CSN(R^{11})_2$, $-N(R^{12})CSR^{11}$, $-N(R^{12})C(O)OR^{11}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{3-7} cyclicamino group optionally containing one or more other $-O-$ or $-S-$ atoms or $-N(R^{12})-$, $-C(O)-$ or $-C(S)-$ groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^{12})SO_2NHet^1$, $-N(R^{12})CONHet^1$, $-N(R^{12})CSNHet^1$, $-SO_2N(R^{12})Het$ [where $-Het$ is an optionally substituted monocyclic C_{3-7} carbocyclic group optionally containing one or more other $-O-$ or $-S-$ atoms or $-N(R^{12})-$, $-C(O)-$, $-S(O)-$ or $-S(O)_2-$ groups], $-Het$, $-CON(R^{12})Het$, $-CSN(R^{12})Het$, $-N(R^{12})CON(R^{12})Het$, $-N(R^{12})CSN(R^{12})Het$, $-N(R^{12})SO_2N(R^{12})Het$, aryl or heteroaryl groups; L^2 is a covalent bond or a linker atom or group as hereinbefore defined for L^1 ; Alk^5 is an optionally substituted straight or branched C_{1-6} alkylene chain optionally interrupted by one, two or three $-O-$ or $-S-$ atoms or $-S(O)_n-$ [where n is an integer 1 or 2] or $-N(R^{12})-$ e.g. $-N(CH_3)-$ groups; and r is zero or the integer 1, 2, or 3. It will be appreciated that when two R^{11} or R^{12} groups are present in one of the above substituents the R^{11} and R^{12} groups may be the same or different.

When in the group $-L^2Alk^5(R^{10a})_r$ r is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{10a} may be present on any suitable carbon atom in $-Alk^5$. Where more than one R^{10a} substituent is present these may be the same or different and may be present on the same

or different atom in -Alk^5 . Clearly, when r is zero and no substituent R^{10a} is present the alkylene chain represented by Alk^5 becomes an alkyl group.

When R^{10a} is a substituted amino group it may be for example a group -NHR^{11} [where R^{11} is as defined above] or a group $\text{-N(R}^{11})_2$ wherein each R^{11} group is the same or different.

When R^{10a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{10a} is a substituted hydroxy or substituted thiol group it may be for example a group -OR^{11} or a -SR^{12} group respectively.

The term "arylalkyl" refers to a straight or branched alkyl group, as defined herein, wherein a terminal hydrogen atom is replaced with an aryl group, as defined herein.

The term "aryloxyalkyl" is intended to refer to a straight or branched alkyl group, as defined herein, wherein a terminal hydrogen atom is replaced with an aryl-O- group, where the aryl group is as defined herein.

The term "alkanoyloxyalkyl" refers to a straight or branched alkyl group wherein a terminal hydrogen atom is replaced with an alkyl-C(O)O- group, where the alkyl group is as defined herein.

The term "aroyloxyalkyl" refers to a straight or branched alkyl group, as defined herein, wherein a terminal hydrogen atom is replaced with an aryl-C(O)O- group, where the aryl group is as defined herein.

Esterified carboxyl groups represented by the group R^{10a} include groups of formula $\text{-CO}_2\text{Alk}^6$ wherein Alk^6 is a straight or branched, optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12} aryl C_{1-8} alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12} aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12} aryloxy C_{1-8} alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8} alkanoyloxy C_{1-8} alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12} aroyloxy C_{1-8} alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional

substituents present on the Alk^6 group include R^{10a} atoms and groups as described above.

When Alk^5 is present in or as a substituent it may be for example a $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$ or $-\text{C}(\text{CH}_3)_2\text{CH}_2-$ chain, optionally interrupted by one, two, or three $-\text{O}-$ or $-\text{S}-$, atoms or $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$ or $-\text{N}(\text{R}^{12})-$, e.g. $-\text{N}(\text{CH}_3)-$ groups. The alkylene chains represented by Alk^5 may be optionally substituted by one, two or three halogen atoms in addition to any R^{10a} groups that may be present.

It will be appreciated that when $-\text{NHet}^1$ or $-\text{Het}$ forms part of a substituent the heteroatoms or heteroatom containing groups that may be present within the ring $-\text{NHet}^1$ or $-\text{Het}$ take the place of carbon atoms within the parent carbocyclic ring.

Thus when $-\text{NHet}^1$ or $-\text{Het}$ forms part of a substituent each may be for example an optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on $-\text{NHet}^1$ include those substituents described above for heterocycloaliphatic groups.

Particularly useful atoms or groups represented by R^{10} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6} alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, or thienyl, C_{1-6} hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxy C_{1-6} alkyl, e.g. carboxyethyl, C_{1-6} alkylthio e.g. methylthio or ethylthio, carboxy C_{1-6} alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxy-propylthio, C_{1-6} alkoxy, e.g. methoxy or ethoxy, hydroxy C_{1-6} alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C_{3-7} cycloalkyl, e.g. cyclobutyl, cyclopentyl, C_{5-7} cycloalkoxy, e.g. cyclopentyloxy, halo C_{1-6} alkyl, e.g. trifluoromethyl, halo C_{1-6} alkoxy, e.g. trifluoromethoxy, C_{1-6} alkylamino, e.g. methylamino, ethylamino, $-\text{CH}(\text{CH}_3)\text{NH}_2$ or $-\text{C}(\text{CH}_3)_2\text{NH}_2$, halo C_{1-6} alkylamino, e.g. fluoro C_{1-6} alkylamino, e.g. $-\text{CH}(\text{CF}_3)\text{NH}_2$ or $-\text{C}(\text{CF}_3)_2\text{NH}_2$, amino ($-\text{NH}_2$), amino C_{1-6} alkyl, e.g. aminomethyl or aminoethyl, C_{1-6} dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6} alkylamino C_{1-6} alkyl, e.g. ethylaminoethyl, C_{1-6} dialkylamino C_{1-6}

6alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋₆dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, imido, such as phthalimido or naphthalimido, e.g. 1,8-
 5 naphthalimido, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk⁶ [where Alk⁶ is as defined above], C₁₋₆alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g.
 10 methylaminosulphonyl or ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC₁₋₆alkylaminocarbonyl, e.g. aminoethylamino-
 15 carbonyl, C₁₋₆dialkylaminoC₁₋₆alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C₁₋₆alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylamino-
 20 carbonylmethylamino, aminothiocabonylamino, C₁₋₆alkylaminothiocabonylamino, e.g. methylaminothiocabonylamino or ethylaminothiocabonylamino, C₁₋₆dialkylaminothiocabonylamino, e.g. dimethylaminothiocabonylamino or diethylaminothiocabonylamino, C₁₋₆alkylaminothiocabonylC₁₋₆alkylamino, e.g. ethylaminothiocabonylmethylamino, -CONHC(=NH)NH₂, C₁₋₆alkylsulphonyl-
 25 amino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-NHSO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethyl-
 30 aminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC₁₋₆alkylamino, optionally substituted phenylaminosulphonylamino, C₁₋₆alkanoylamino, e.g. acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoylamino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g.

acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidoethyl-amino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonyl-amino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, 5 benzyloxy-carbonylaminoC₁₋₆alkyl e.g. benzyloxycarbonylaminoethyl, benzothio, pyridyl-methylthio or thiazolylmethylthio groups.

Where desired, two R¹⁰ substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C₁₋₆alkylenedioxy group such as methylenedioxy or ethylenedioxy.

10 It will be appreciated that where two or more R¹⁰ substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position on the aromatic or heteroaromatic group.

The presence of certain substituents in the compounds of formulae (1), 15 (1A) and (2) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, 20 hydroiodides, alkylsulfonates, e.g. methanesulfonates, ethanesulfonates, or isothionates, arylsulfonates, e.g. p-toluenesulfonates, besylates or napsylates, phosphates, sulfates, hydrogen sulfates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

25 Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention 30 include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

In one particular group of compounds of formula (2), and in the processes hereinafter R¹ is an optionally substituted phenyl, monocyclic heteroaryl or C₃₋₇cycloalkyl group especially an optionally substituted phenyl,

pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, thienyl, indolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or group. Especially preferred is when R^1 is an optionally substituted phenyl or cyclopropyl group.

Each of the preferred R^1 cycloalkyl groups may be unsubstituted. When substituents are present these may in particular include halogen atoms, especially fluorine, chlorine or bromine atoms, or C_{1-6} alkyl groups, especially C_{1-3} alkyl groups, most especially a methyl group, or a halo C_{1-6} alkyl group, especially a fluoro C_{1-6} alkyl group, most especially a $-CF_3$ group, or a C_{1-6} alkoxy, especially methoxy, ethoxy, propoxy or i-propoxy group, or a halo C_{1-6} alkoxy, especially a fluoro C_{1-6} alkoxy, most especially a $-OCF_3$ group, or a cyano ($-CN$), esterified carboxyl, especially $-CO_2CH_3$ or $-CO_2C(CH_3)_3$, nitro ($-NO_2$), amino ($-NH_2$), substituted amino, especially $-NHCH_3$ or $-N(CH_3)_2$, $-C(O)R^6$, especially $-C(O)CH_3$, or $-N(R^6)C(O)R^7$, especially $-NHCOCH_3$ group.

Particularly preferred optional substituents which may be present on R^1 aromatic or heteroaromatic groups include one, two or three atoms or groups $-R^{10a}$ or $-L^6Alk^5(R^{10a})_r$ as hereinbefore defined. Particularly useful optional substituents include halogen atoms, especially fluorine, chlorine or bromine atoms, or C_{1-6} alkyl groups, especially C_{1-3} alkyl groups, most especially a methyl group, or a halo C_{1-6} alkyl group, especially a fluoro C_{1-6} alkyl group, most especially a $-CF_3$ group, or a C_{1-6} alkoxy, especially methoxy, ethoxy, propoxy or i-propoxy group, or a halo C_{1-6} alkoxy, especially a fluoro C_{1-6} alkoxy, most especially a $-OCF_3$ group, or a cyano ($-CN$), carboxyl ($-CO_2H$), esterified carboxyl ($-CO_2Alk^6$), especially $-CO_2CH_3$, $-CO_2CH_2CH_3$, or $-CO_2C(CH_3)_3$, nitro ($-NO_2$), amino ($-NH_2$), substituted amino, especially $-NHCH_3$ or $-N(CH_3)_2$, $-COR^{11}$, especially $-COCH_3$, or $-N(R^{12})COR^{11}$, especially $-NHCOCH_3$ group.

Further preferred optional substituents which may be present on R^1 aromatic or heteroaromatic groups include groups of formula $-L^6Alk^5(R^{10a})_r$ in which r is the integer 1 or 2, L^6 is a covalent bond or an $-O-$ or $-S-$ atom or a $-N(R^3)-$, especially $-NH-$ or $-N(CH_3)-$, $-C(O)-$, $-C(S)-$, $-C(O)O-$, $-OC(O)-$, $-N(R^3)CO-$, especially $-NHCO-$, or $-CON(R^3)-$, especially $-CHNH-$ group, Alk^5 is a C_{1-6} alkyl chain, especially a $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$ chain and R^{10a} is a hydroxyl or substituted hydroxyl group,

especially a $-OCH_3$, $-OCH_2CH_3$ or $-OCH(CH_3)_2$ group or a $-NH_2$ or substituted amino group, especially a $-N(CH_3)_2$ or $-N(CH_2CH_3)_2$ group or a $-Het$ group, especially an optionally substituted monocyclic C_{3-7} carbocyclic group containing one, two or three $-O-$, $-S-$, $-N(R^{12})-$, especially $-NH-$ or $-N(CH_3)-$ or $-C(O)-$ groups within the ring structure as previously described, most especially an optionally substituted pyrrolidinyl, imidazolidinyl, piperidinyl, e.g. N-methylpiperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group or R^{10a} is an optionally substituted heteroaromatic group, especially a five- or six-membered monocyclic heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms, such as optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, triazolyl, pyridyl, pyrimidinyl, triazinyl, pyridazinyl, or pyrazinyl group. Particularly preferred optional substituents on the $-Het$ groups just described include hydroxyl ($-OH$) and carboxyl ($-CO_2H$) groups or those preferred optional substituents just described in relation to the group R^1 , especially when R^1 is a cycloalkyl group.

In one particularly preferred group of compounds of formula (2) R^1 is an optionally substituted phenyl group, especially a phenyl group optionally substituted by one, two or three substituents where at least one, and preferably two substituents are located *ortho* to the bond joining R^1 to the remainder of the compound of formula (2). Particularly preferred *ortho* substituents include halogen atoms, especially fluorine or chlorine atoms, or C_{1-3} alkyl groups, especially methyl groups, C_{1-3} alkoxy groups, especially methoxy, halo C_{1-3} alkyl groups, especially $-CF_3$, halo C_{1-3} alkoxy groups, especially $-OCF_3$, or cyano ($-CN$), groups. In this class of compounds a second or third optional substituent when present in a position other than the *ortho* positions of the ring R^1 may be preferably an atom or group $-R^{10a}$ or $-L^6Alk^5(R^{10a})_r$ as herein generally and particularly described. In another preference, the R^1 phenyl group may have a substituent *para* to the bond joining R^1 to the remainder of the compound of formula (2). Particular *para* substituents include those particularly preferred *ortho* substituents just described. Where desired, the *para* substituent may be present with other *ortho* or *meta* substituents as just mentioned.

Typical examples of the group R^1 include phenyl, 3-methylphenyl, 4-methylphenyl, 2-chlorophenyl and cyclopropyl, especially phenyl.

In one particular group of compounds of formula (2), and in the processes hereinafter, each R^y is preferably a hydrogen atom.

5 Particular examples of the group $-CO_2Alk^2$ include those groups as defined hereinbefore for $-CO_2Alk^6$. More especially, Alk^2 in compounds of formula (2), and in the processes hereinafter is preferably a C_{1-6} alkyl group.

Particular examples of the group R include $-CN$, NO_2 , $-CO_2C_{1-6}alkyl$, $-COC_{1-6}alkyl$ or $-CONHet_2$ groups. R in compounds of formula (2), and in the
10 processes hereinafter, is preferably a $-CN$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-COCH_3$ or $-CONHet^2$ group.

Particular examples of the group $-NHet^2$ include optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl or thiazolidinyl groups. In one particular
15 group of compounds $-NHet^2$ is an optionally substituted pyrrolidinyl group.

Particularly preferred $-NHet^2$ substituents include one, two, three or four groups, which may be the same or different, selected from $-OH$, $-(Alk^{3a})OH$ (where Alk^{3a} is a straight or branched C_{1-4} alkylene chain), $-OR^{7a}$ (where R^{7a} is a straight or branched C_{1-6} alkyl group), $-(Alk^{3a})OR^{7a}$, $-NR^{7b}R^{8a}$ (where R^{7b} and R^{8a} may be the same or different and is each independently a
20 hydrogen atom or straight or branched C_{1-6} alkyl group), $-(Alk^{3a})NR^{7b}R^{8a}$ or straight or branched C_{1-6} alkyl group, or protected derivatives thereof. Each substituent may be present on any ring carbon atom. In one particular class of compounds of formula (2) one or two substituents are present, in the latter
25 instance on separate ring carbon atoms. More particular R^d substituents include $-OH$, $-CH_2OH$, $-CH(CH_3)OH$ or $-C(CH_3)_2OH$ groups or protected derivatives thereof. R^d is especially a $-OH$ or $-CH_2OH$ group. Particular examples of suitable protecting groups include esters such as methyl or ethyl ester or benzyl ethers, for example, paramethoxy benzylether or benzyl ether
30 or ethers such as tetrahydropyran-2-yl ether or alkyl ethers e.g. methoxy. Typically the protecting group is a C_{1-6} alkyl, especially methyl, benzyl or tetrahydropyran-2-yl group, especially a tetrahydropyran-2-yl group.

Typical examples of the group R include $-CN$, $-CO_2CH_2CH_3$ and $-COPyrrolidin-1-yl$. Further examples include $-CO[3-(tetrahydropyran-2-$

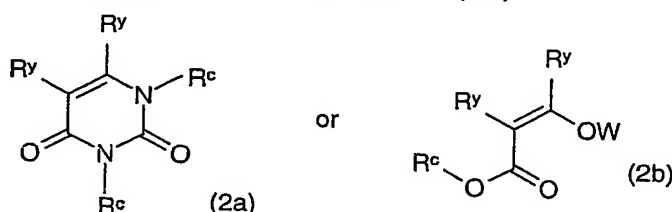
loxy)]pyrrolidin-1-yl or $-\text{CO}[2-(\text{hydroxymethyl})]\text{pyrrolidin-1-yl}$. In a particular embodiment R is $-\text{CN}$.

It will be appreciated that these particular preferences may also apply to the resulting halides of formula (1) and compounds of formula (1A).

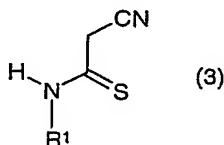
5 The novel intermediates of formula (2) may be prepared by any number of processes. One particular process involves the use of a uracil derivative of formula (2a) or an hydroxy acrylic acid derivative of formula (2b):

Thus, in another aspect of the invention we provide a process for the manufacture of a compound of formula (2) comprising the steps of:

10 a) reacting a compound of formula (2a) or (2b):

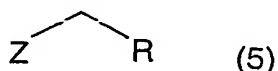


wherein R^y is as defined herein, R^c is an optionally substituted alkyl group, W is a hydrogen atom or metal ion or amine salt; with a compound of formula (3):



15 wherein R^1 is as defined herein;

b) followed by reaction with a compound of formula (5):



wherein R is as herein defined and Z is a leaving group.

20 As used herein the term "leaving group" is intended to include any group which may be displaced during the course of a reaction. Examples include halogen atoms, e.g. a fluorine, bromine, iodine or chlorine atom or sulfonyloxy groups such as an alkylsulfonyloxy, e.g. trifluoromethylsulfonyloxy or arylsulfonyloxy, e.g. p-toluenesulfonyloxy groups. Particularly preferred Z
25 groups include halogen atoms, especially chlorine or bromine.

Examples of the group W in compounds of formula (4) include H, metal ions such as Li, Na or K, amine salts such as triethylamine or N,N-

diisopropylethylamine or N-methylmorpholine. In one particular aspect of the process W is a metal ion, especially Na.

Particular examples of the group R^o include C₁₋₃ alkyl groups, especially methyl.

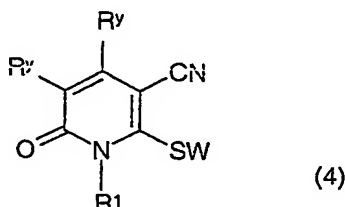
5 Thus, in step a) of the process of the invention a compound of formulae (2a) or (2b) is reacted with a thioamide of formula (3). The reaction may be performed in the presence of a base. Appropriate bases may include, but are not limited to, lithium bases such as n-butyl or t-butyl lithium or lithium diisopropylamide (LDA), or silazanes e.g. lithium hexamethyldisilazane
 10 (LiHMDS) or sodium hexamethyldisilazane (NaHMDS), or a carbonate, e.g. potassium carbonate, an alkoxide, e.g. sodium ethoxide, sodium methoxide, potassium t-butoxide, a hydroxide e.g. NaOH or a hydride, e.g. sodium hydride, or an organic amine e.g. triethylamine or N,N-diisopropylethylamine or a cyclic amine, such as N-methylmorpholine or pyridine. The reaction may
 15 be performed in an organic solvent such as an amide e.g. a substituted amide such as dimethylformamide, an ether e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol e.g. methanol, ethanol or propanol or acetonitrile, at a temperature from ambient to the reflux temperature. In one particular aspect of the process the reaction is achieved using an alkoxide
 20 base, especially sodium ethoxide or sodium methoxide in an alcoholic solvent, especially ethanol at reflux temperature.

Intermediates of formula (2a), where not commercially available, may be prepared using standard methodology. (See, for example, Mir Hedayatullah, J. Heterocyclic Chem., 18, 339, (1981)). Similarly,
 25 intermediates of formula (2b) where not commercially available, may be prepared using standard methodology. For example they may be prepared *in-situ* by reaction of an ester e.g. ethyl acetate with a base such as sodium methoxide followed by addition of a formate e.g. methyl formate.

In a similar manner, Intermediates of formula (3), if not commercially
 30 available, may be prepared using methods known to those skilled in the art (see, for example Adhikari et al, Aust. J. Chem., 52, 63-67, (1999)). For example, an isothiocyanate of formula R¹NCS may be reacted with acetonitrile in the presence of a base e.g. NaHMDS in a suitable solvent e.g.

tetrahydrofuran, optionally at a low temperature, e.g. around -78°C . According to the nature of the group R^1 , the Intermediate of formula (3) may be prepared *in situ*, for example, using the methods as described herein, followed by subsequent addition of a compound of formulae (2a) or (2b).

5 During the course of this process an intermediate of formula (4) may be formed:

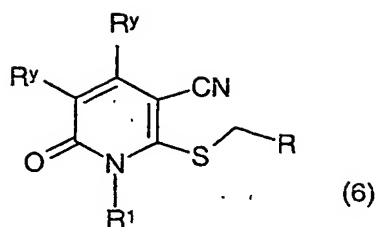


If desired the intermediate may be isolated at the end of step a) and subsequently reacted with intermediate (5) to form the desired amine. In some instances however it may be advantageous not to isolate the intermediate of formula (4) and reaction b) may be carried out directly with the reaction mixture of step a).

15 If a different solvent is used during step b) of the process, it may be necessary to evaporate the solvent, *in vacuo*, from the first stage of the process before proceeding with the second stage. Once evaporated, the crude solids from step a) may be used in the next stage or they may be purified, for example, by crystallisation, to yield an isolated intermediate, such as a compound of formula (4).

20 During step b) of the process an intermediate of formula (5) may then be added to the reaction mixture or to the crude solids or purified product from step a) in a suitable solvent. Suitable solvents include, but are not limited to, amides e.g. a substituted amide such as dimethylformamide, alcohols e.g. ethanol, methanol or isopropyl alcohol, ethers e.g. a cyclic ether such as tetrahydrofuran or dioxane or acetonitrile. In one particular aspect of the process the reaction is carried out in acetonitrile. The reaction may be performed at a temperature from ambient up to the reflux temperature.

25 During the course of step b) an intermediate of formula (6):



may be observed or even isolated, depending upon the nature of the group R. The intermediate of formula (6) may be converted to a compound of formula (1) using the methods described above. In this situation it may be necessary to add a base, in order for the reaction to proceed to completion. Appropriate bases include carbonates e.g. caesium or potassium carbonate, or alkoxides e.g. potassium *t*-butoxide, or hydrides e.g. sodium hydride or organic amines e.g. triethylamine or N,N-diisopropylethylamine or cyclic amines, such as N-methylmorpholine or pyridine.

The intermediates of formulae (4) and (6) are novel and each form a further aspect of the invention.

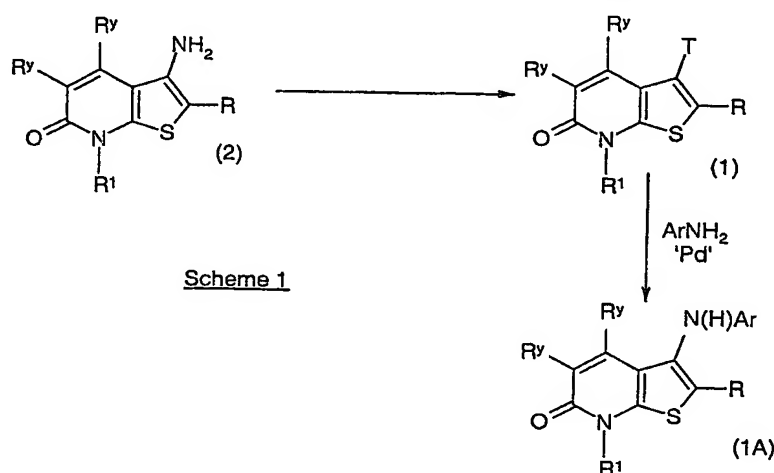
It will be appreciated that intermediates of formula (5) where not commercially available may be prepared using standard methods known to those skilled in the art. For example, alcohol groups may be converted into leaving groups, such as halogen atoms or sulfonyloxy groups using conditions known to the skilled artisan. For example, an alcohol may be reacted with thionyl chloride in a halogenated hydrocarbon e.g., dichloromethane to yield the corresponding chloride. A base e.g., triethylamine may also be used in the reaction.

It will be appreciated that intermediates, such as intermediates (2a), (2b), (3) or (5), if not available commercially, may also be prepared by methods known to those skilled in the art following procedures set forth in references such as Rodd's Chemistry of Carbon Compounds, Volumes 1-15 and Supplementals (Elsevier Science Publishers, 1989), Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-19 (John Wiley and Sons, 1999), Comprehensive Heterocyclic Chemistry, Ed. Katritzky et al, Volumes 1-8, 1984 and Volumes 1-11, 1994 (Pergamon), Comprehensive Organic Functional Group Transformations, Ed. Katritzky et al, Volumes 1-7, 1995 (Pergamon), Comprehensive Organic Synthesis, Ed. Trost and Fleming, Volumes 1-9, (Pergamon, 1991), Encyclopedia of Reagents for Organic

Synthesis Ed. Paquette, Volumes 1-8 (John Wiley and Sons, 1995), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989) and March's Advanced Organic Chemistry (John Wiley and Sons, 1992).

Where desired the process according to the invention may be extended by optionally employing one or more subsequent reactions to convert a compound of formula (2) to a further compound of formula (2), for example, using methods as described hereinafter.

The process according to the invention is particularly useful for manufacturing certain halides of formula (1). These may then be converted into compounds of formula (1A), for example, as shown in Scheme 1 below.

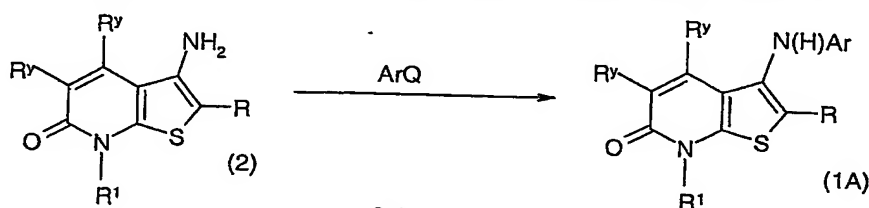


Thus in Scheme 1 a compound of formula (1A) may be prepared by reaction of a compound of formula (1) with an amine ArNH_2 in the presence of a transition metal catalyst, e.g. a palladium catalyst. The reaction may be conveniently carried out in a solvent such as toluene or ethylene glycol dimethyl ether at an elevated temperature, e.g. the reflux temperature, using a catalyst such as tris(dibenzylideneacetone)dipalladium(0), a phosphine ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or tri-*tert*-butylphosphine and a base such as caesium carbonate or tripotassium phosphate. Where desired, alternative reaction conditions may be used, for example as described in the literature [Luker et al. Tet. Lett. (2001) 41, 7731; Buchwald S.L. J.Org.Chem. (2000) 65 1144; Hartwig J.F. Angew. Chem. Int. Ed. Engl. (1998) 37, 2046].

Intermediates of formula (1) in Scheme 1 may be obtained by standard methods such as for example by the Sandmeyer reaction. Thus for example a

halide of formula (1) may be prepared by treatment of a compound of formula (2) with a diazotization reagent e.g. an alkyl nitrite, for example *t*-butyl nitrite or sodium nitrite in the presence of an acid e.g. sulphuric acid or hydrochloric acid, followed by addition of a source of halide such as a copper salt, for example copper (II) bromide, copper (II) chloride or copper (II) iodide in the presence of a solvent, for example a nitrile such as acetonitrile at a temperature from about 0° to around 65°C. In one particular aspect of the process T is a bromine atom.

Alternatively, in a further aspect of the invention a compound of formula (1A) may be prepared according to the reactions set out in Scheme 2 below.



Thus in Scheme 2 a compound of formula (1A) may be prepared by reaction of a compound of formula (2) with a compound ArQ, wherein Q is a leaving group, in the presence of a transition metal catalyst e.g. a palladium catalyst. The reaction may be conveniently carried out in a solvent such as toluene or ethylene glycol dimethyl ether at an elevated temperature, e.g. the reflux temperature, using a catalyst such as tris(dibenzylideneacetone)dipalladium(0), a phosphine ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or tri-*tert*-butylphosphine and a base such as caesium carbonate or tripotassium phosphate. Where desired, alternative reaction conditions may be used, for example as described in the literature [Luker et al. Tet. Lett. (2001) 41, 7731; Buchwald S.L. J.Org.Chem. (2000) 65 1144; Hartwig J.F. Angew. Chem. Int. Ed. Engl. (1998) 37, 2046]. In one particular aspect of the process Q is a halogen atom, especially a bromine atom.

In an alternative embodiment a copper catalyst, e.g. copper(I) iodide, may be employed. The reaction may be performed in the presence of a base, e.g. tripotassium phosphate, optionally in a suitable solvent such as an alcohol, e.g. isopropanol, or an ether, e.g. 1,4-dioxane. A chelating ligand

such as ethylene glycol or *N,N*-dimethylethanolamine may also be used. In reactions of this type Q is typically a halogen atom, especially an iodine atom.

It will be appreciated that the compounds of formulae (1) or (1A), such as those as formed in the process as defined herein, or any preceding intermediates may be further derivatised during the processes described above by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Such reactions are optional additional process steps to those described above, and the invention is to be understood to extend to such optional steps. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of any of formula (1) or (1A) or any preceding intermediates where appropriate functional groups exist in these compounds.

Thus, for example if the group R^y is present this may be removed to give a hydrogen atom, using standard methods known to those skilled in the art. For example, decarboxylation using copper in the presence of quinoline may be employed to remove carboxylic acids. Halogen atoms may be removed, for example, using Friedel-Crafts catalysts, such as $AlCl_3$, or by hydrogenation.

Ester groups such as $-CO_2Alk^2$ in the compound of formulae (1), (1A) and intermediates thereto may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed hydrolysis depending on the nature of the group Alk^2 . Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an organic solvent e.g. dichloromethane or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

Amides may be prepared from the corresponding acid, using standard methodology. For example, an acid chloride $-COCl$ (prepared from the corresponding acid using methods known to those skilled in the art) may be reacted with a secondary amine in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or *N*-methylmorpholine, in

a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or a dipolar aprotic solvent such as an amide, e.g. dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran, at for example ambient temperature. Alternatively, an acid may be reacted with
5 a primary or secondary amine in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively an acid may be reacted with a
10 chloroformate, for example ethylchloroformate, prior to the desired reaction with a secondary amine.

Nitriles may be hydrolysed to give primary amides, for example using a base such as a hydroxide e.g. sodium hydroxide in for example water and an alcohol e.g. ethanol.

15 Further interconversions are discussed in co-pending PCT application number PCT/GB03/02667.

N-oxides may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated
20 temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts may be prepared by reaction with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an
25 ether e.g. diethyl ether, or an alcohol, e.g. ethanol, using conventional procedures.

Where it is desired to obtain a particular enantiomer this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

30 Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers, e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the

desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes of the invention described above. Alternatively, a particular enantiomer may be obtained by performing an enantiomer specific enzymatic biotransformation e.g. an ester hydrolysis using an esterase and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following examples illustrate the present invention in more detail; however, they are not intended to limit its scope in any manner.

All temperatures are in °C. The following abbreviations are used:

EtOAc - ethyl acetate;

DCM - dichloromethane;

MeOH - methanol;

MeCN - acetonitrile;

EtOH - ethanol;

Et₂O - diethyl ether;

DMSO - dimethylsulphoxide;

THF - tetrahydrofuran;

H₂O - water;

r.t. - room temperature;

NaHMDS - sodium bis(trimethylsilyl)amide;

CDCl₃ - deuterated chloroform;

MIBK - 4-methyl-2-pentanone;

DME - ethylene glycol dimethyl ether;

BINAP - 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl;

Pd₂(dba)₃ - tris(dibenzylideneacetone)dipalladium(0);

EDTA - ethylenediaminetetraacetic acid.

All NMR's were obtained either at 300MHz or 400MHz. All Intermediates and Examples were named with the aid of Beilstein Autonom (available from MDL Information Systems GmbH, Therdor-Heuss-Allee 108D 60486, Frankfurt, Germany) or were given names that seemed consistent.

LCMS retention times (RT) quoted were generated on a Hewlett Packard 1100/ThermoFinnigan LCQ Duo LC/MS system using Electrospray

ionisation and the following LC method: Phenomenex Luna C₁₈(2) 5 μ 100mm x 4.6mm column; mobile phase A = 0.08% formic acid in water; mobile phase B = 0.08% formic acid in MeCN; flow rate of 3.0 mLmin⁻¹, column temperature 35°C.

5 Gradient:-

Time (min)	%A	%B
0.00	95.0	5.0
4.40	5.0	95.0
5.30	5.0	95.0
5.32	95.0	5.0
6.50	95.0	5.0

10 Gas Chromatographs were run on a Perkin Elmer Autosystem instrument, using an SGE 25QC2 BP5 1.0 column. Initial temperature, 70 °C, heat at 15 °C/min to 250 °C, hold 10 min. Injector temperature 150 °C, detector temperature 250 °C.

Intermediate 1

2-Cyano-N-phenylthioacetamide

15 The title compound was prepared according to Adhikari et al, Australian J. Chem., 1999, 52, 63-67. δ H (DMSO-d₆) 11.95 (1H, br s), 7.80 (2H, d, \downarrow 7.4Hz), 7.45 (2H, dd, \downarrow 7.4Hz, 7.4Hz), 7.30 (1H, t, \downarrow 7.4Hz), 4.29 (2H, s).

Intermediate 2

2-Chloro-1-pyrrolidin-1-yl-ethanone

20 The title compound was prepared according to US2788202. δ H (CDCl₃) 4.04 (2H, s), 3.55 (4H, m), 2.1-1.85 (4H, m).

Intermediate 3

(R)-3-(Tetrahydropyran-2-yloxy)pyrrolidine

25 Methyl formate (23 ml) was added dropwise over 15 min to a cooled solution of of (R)-pyrrolidin-3-ol (25 g) in MeOH (12 ml), maintaining the temperature at below 15 °C. Once the addition was complete, the reaction was stirred for a further 30 min. GC analysis showed the reaction was complete. The excess MeOH and methyl formate were removed by concentration under vacuum on.

a rotary evaporator. Toluene (50 ml) was added and the mixture concentrated again to ensure complete removal. The (R)-3-hydroxy-pyrrolidine-1-carbaldehyde was obtained in a 96 % yield (32.3 g), 99 % pure by GC, RT 10.0 min. δ H (CDCl₃) 8.20 and 8.25 (2H, 2 x s), 4.45-4.60 (1H,m), 3.40-3.80 (4H,m), 1.90-2.10 (2H,m).

The (R)-3-hydroxypyrrolidine-1-carbaldehyde (31 g) was treated with dihydropyran (36.8 ml) and p-toluenesulphonic acid (1 g). The mixture was stirred at room temperature for approximately one hour, during which time the colour changed from yellow to dark purple. GC analysis showed the reaction was complete. The reaction was quenched by addition of saturated sodium bicarbonate solution (90 ml). The aqueous phase was extracted with DCM (3 x 90 ml). The combined organic phase was washed with saturated sodium chloride solution (90 ml), then dried over MgSO₄ and concentrated at below 30 °C. The product, 3-(tetrahydropyran-2-yloxy)pyrrolidine-1-carbaldehyde was obtained in 100 % yield, 54.5 g. GC analysis showed two adjacent peaks, RT 14.45 and 14.83 min, 49.7 and 47.1 % respectively. δ H (CDCl₃) 8.22 and 8.27 (1H, 2 x s), 4.60-4.75 (1H, m), 4.35-4.50 (1H, m), 3.80-3.95 (1H, m), 3.40-3.70 (5H, m), 1.40-2.20 (8H, m).

A solution of KOH (5 g) in water (50 ml) was added to 3-(tetrahydropyran-2-yloxy)pyrrolidine-1-carbaldehyde. The mixture was heated at 50 °C for approximately one hour, after which time GC analysis showed the reaction was complete. After cooling to room temperature, the product was extracted with DCM (3 x 50 ml). The organic phase was dried over MgSO₄ and concentrated. The title compound was obtained in 100 % yield, (8.5 g). GC analysis, RT 10.4 min, 96.6 % purity. δ H (CDCl₃) 4.60-4.70 (1H, m), 4.35-4.45 (1H, m), 3.80-3.95 (1H, m), 3.40-3.60 (1H, m), 2.90-3.25 (4H, m), 1.40-2.05 (8H, m).

Intermediate 4

2-Chloro-1-[(R)-3-(tetrahydropyran-2-yloxy)pyrrolidin-1-yl]ethanone

Intermediate 3 (2g) was dissolved in DCM (30 ml) and cooled using an ice/water bath. Diisopropylethylamine (2.3 ml) was added. Chloroacetyl chloride (0.93 ml) was added dropwise over 1 hour, maintaining the temperature below 7 °C. When the addition was complete, NaHCO₃ (30 ml, 5

% w/v) was added. The mixture was stirred and allowed to warm to room temperature for one hour. The phases were separated, the organic phase was dried over MgSO₄ and concentrated. The title compound was obtained in a 93 % yield (2.6 g) as a brown oil. δ H (CDCl₃) 4.60-4.75 (1H, m), 4.40-4.55 (1H, m), 3.95-4.15 (2H, m), 3.45-3.95 (6H, m), 1.45-2.30 (8H, m). LCMS (ES⁺) RT 2.54 min, 248 (M+H)⁺.

Intermediate 5

2-Chloro-1-((S)-2-hydroxymethylpyrrolidin-1-yl)ethanone

The title compound was prepared according to the method described in Nicolaides et al, J. Med. Chem. 1986, 29, 959-971.

Example 1

Sodium 3-cyano-6-oxo-1-phenyl-1,6-dihydropyridine-2-thiolate

Method A

A solution of sodium methoxide in MeOH (30 wt%, 202.2g) was added to absolute EtOH (360mL) followed by 1,3-dimethyluracil (75g) and 2-cyano-N-phenylthioacetamide (90g). The resulting mixture was heated at reflux for 8h and then allowed to cool to ambient temperature overnight. The reaction mixture was then cooled to +5° and maintained at this temperature for at least an hour when the product was recovered by filtration. The filter cake was washed with cold (+5°) absolute EtOH (450ml) and then dried to constant weight under vacuum at 45° to give the title compound as a pale pink solid (130.0g). The product thus obtained contains residual EtOH and MeOH, estimated at 12.2 wt% by ¹H NMR, corresponding to a corrected yield of 114.1g. δ H (DMSO-d₆) 7.32 (2H, m), 7.27-7.18 (1H, m), 7.16 (1H, d, \downarrow 9.1Hz), 6.92 (2H, m), 5.63 (1H, d, \downarrow 9.1Hz). LCMS (ES⁺) RT 2.43 minutes, 229 (M+H)⁺.

Method B

Sodium methoxide (2.88g) was added to EtOAc (8.7mL), cooled to +14°. To the resulting suspension was added methyl formate (2.2mL) slowly over 4.3h whilst maintaining the reaction temperature at +14°. After this time, the temperature was adjusted to +25° and the reaction was allowed to stir out at this temperature overnight. Absolute EtOH (25mL) and a solution of sodium

methoxide in MeOH (30 wt%, 6.7mL) were then added followed by 2-cyano-*N*-phenyl-thioacetamide (5g) and the resulting mixture was heated at reflux for 24h. The reaction was cooled to +5° when the product was recovered by filtration. The filter cake was washed with cold (+5°) absolute EtOH (20ml) and then dried to constant weight under vacuum at 45° to give the title compound as a pale pink solid (2.77g; equivalent to 2.63g at 100%). δ H (DMSO-*d*₆) 7.32 (2H, m), 7.27-7.18 (1H, m), 7.16 (1H, d, *J* 9.1Hz), 6.92 (2H, m), 5.63 (1H, d, *J* 9.1Hz). LCMS (ES⁺) RT 2.43 minutes, 229 (M+H)⁺.

Example 2

Sodium 1-(2-chlorophenyl)-3-cyano-6-oxo-1,6-dihydropyridine-2-thiolate

NaHMDS (13.2mL, 1.0M in THF, 13.2mmol) was added slowly to a solution of 2-chlorophenyl isothiocyanate (1.02g, 6.0mmol) in THF (50mL) and acetonitrile (5mL) at -78 °C. The mixture was warmed to r.t. over 1h. *N,N*-Dimethyluracil (841mg, 6.0mmol) and EtOH (75mL) were added and the mixture heated at reflux for 4h. Volatiles were removed *in vacuo* and the residue was dissolved in hot EtOH (10mL). Et₂O (~100mL) was added slowly to precipitate out the product. The solid was filtered off, washed with Et₂O (2 x 30mL) and dried to give the title compound (1.5g, 88%)(v. hygroscopic). δ H (DMSO-*d*₆) 7.35-7.32 (1H, m), 7.25-7.20 (2H, m), 7.15 (1H, d, *J* 9.1Hz), 7.05-7.01 (1H, m), 5.85 (1H, br s), 5.58 (1H, d, *J* 9.1Hz). LCMS (ES⁺) RT 3.06 minutes, 285 (M+H)⁺.

Example 3

3-Amino-6-oxo-7-phenyl-6,7-dihydro-thienof[2,3-*b*]pyridine-2-carbonitrile

A mixture of Example 1 (100g at 100%) and chloracetonitrile (30.4 mL) in MeCN (500 mL) was heated at reflux for 2h. The mixture was cooled, initially to 40° when water (300mL) was added, and then to +10°. The reaction was maintained at +10° for at least 1h when the product was recovered by filtration. The filter cake was washed with cold (+10°) H₂O (500mL) followed by a cold (+10°) mixture of MeCN and H₂O (1:1, 300mL). The product was dried under vacuum at 50° to constant weight to give the title compound as an off-white solid (100.9g). δ H (DMSO-*d*₆) 7.90 (1H, d, *J* 9.6Hz), 7.46-7.33 (3H, m), 7.25 (2H, m), 6.95 (2H, br s), 6.35 (1H, d, *J* 9.6Hz). LCMS (ES⁺) RT 2.69 minutes, 268 (M+H)⁺.

Example 4

3-Amino-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylic acid ethyl ester

A mixture of Example 1 (0.34g at 100%) and ethyl bromoacetate (0.197mL) in EtOH (6mL) were stirred at room temperature for 1h. H₂O (10mL) was then added. The solid was filtered and washed with more H₂O (2mL). The product was dried under vacuum at 40° to constant weight to give the title compound as a pale pink solid (0.35g). δ H (DMSO-d₆) 8.2 (1H, d, J 9.6Hz), 7.6 (3H, m), 7.45 (2H, m), 7.15 (2H, br s), 6.55 (1H, d, J 9.6Hz), 4.15 (2H, q, J 7.1Hz), 1.2 (3H, t, J 7.1Hz). LCMS (ES⁺) RT 3.29 minutes, 315 (M+H)⁺.

Example 5

3-Amino-7-(2-chlorophenyl)-6-oxo-6,7-dihydrothieno[2,3-b]pyridine-2-carbonitrile

Method A

Chloroacetonitrile (0.35mL, 5.5mmol) was added to a solution of example 2 (1.42g, 5.0mmol) in MeCN (50mL) and the mixture heated at 40 °C for 3h. H₂O (100mL) was added and the mixture concentrated *in vacuo* to remove some of the MeCN (remaining volume ~120mL). The mixture was cooled to 0 °C and the solid filtered off, washed with H₂O (15mL) and Et₂O (2 x 15mL) and dried to give the title compound as a pale brown solid (505mg, 32%). δ H (DMSO-d₆) 8.10 (1H, d, J 9.7Hz), 7.75-7.73 (1H, m), 7.65-7.54 (3H, m), 7.14 (2H, br s, NH₂), 6.54 (1H, d, J 9.7Hz). LCMS (ES⁺) RT 2.97 minutes, 302 (M+H)⁺.

Method B

MeCN (10mL) was added to a solution of NaHMDS (100mL, 1.0M in THF, 100mmol) in THF (50mL) at -78°C to give a thick white precipitate. 2-Chlorophenyl isothiocyanate (7.72g, 45.45mmol) was added to give a brown solution. The mixture was allowed to warm to r.t. over 1h then diluted with EtOH (50mL). N,N-Dimethyluracil (6.4g, 45mmol) was added and the mixture heated at reflux for 24h. Volatiles were removed *in vacuo* and the residue dissolved in MeCN (100mL). Chloroacetonitrile (2.85mL, 45mmol) was added and the mixture heated at 50°C for 1h, a second charge of chloroacetonitrile (2.85mL, 45mmol) was added and heating continued for 1.5h. Some of the

MeCN (~50mL) was removed *in vacuo* and H₂O was added to precipitate the product. The brown solid was filtered off, washed with H₂O (50mL) and Et₂O (50mL) and dried to give the title compound as a brown solid (14.3g, quant.). δ H (DMSO-d₆) 8.10 (1H, d, J 9.7Hz), 7.75-7.73 (1H, m), 7.65-7.54 (3H, m), 7.14 (2H, br s, NH₂), 6.54 (1H, d, J 9.7Hz). LCMS (ES⁺) RT 2.97 minutes, 302 (M+H)⁺.

Example 6

Sodium 3-cyano-1-(2-methylphenyl)-6-oxo-1,6-dihydropyridine-2-thiolate

A solution of NaHMDS (84mL of a 1.0M solution in THF, 84mmol) was added to a solution of o-tolyl isothiocyanate (5.0g, 33.5mmol) and MeCN (18mL) in THF (100mL) at -78 °C. The mixture was allowed to warm to r.t. over 3h. N,N-Dimethyluracil (4.62g, 33mmol) and EtOH (75mL) were added and the mixture heated at reflux for 3h then stirred at r.t. overnight. Volatiles were removed *in vacuo*. The residue was used crude in the next step without further purification.

Example 7

3-Amino-7-(2-methylphenyl)-6-oxo-6,7-dihydrothieno[2,3-b]pyridine-2-carbonitrile

A mixture of crude Example 6 (half of material obtained above) and chloroacetonitrile (1.94mL) in MeCN (25mL) was heated at reflux for 5h. Volatiles were removed *in vacuo*. The residue was treated with H₂O to give a solid which was filtered off and dried to give the title compound (3.0g). δ H (DMSO-d₆) 8.16 (1H, d, J 9.6Hz), 7.7-7.5 (4H, m), 7.19 (2H, s), 6.6 (1H, d, J 9.6Hz), 2.0 (3H, s). LCMS (ES⁺) RT 2.932 minutes, 281.9 (M+H)⁺.

Example 8

Sodium 3-cyano-1-(4-methylphenyl)-6-oxo-1,6-dihydropyridine-2-thiolate

NaHMDS (36.8mL, 1.0M in THF, 36.8mmol) was added slowly to a solution of 4-tolyl isothiocyanate (2.5g, 16.75mmol) in THF (30mL) and MeCN (5mL) at -78 °C. The mixture was warmed to r.t. over 1h. N,N-Dimethyluracil (2.35g, 16.75mmol) and EtOH (20mL) were added and the mixture heated at reflux for 4h. Volatiles were removed *in vacuo* and the residue was dissolved in EtOH (6mL). Et₂O (~60mL) was added slowly to produce a fine, off-white solid. The suspension was cooled to 0 °C and the solid filtered off, washed

with Et₂O and dried to give the title compound as an off-white solid (1.7g, 39%). δ H (DMSO-d₆) 7.15-7.12 (3H, m), 6.80-6.77 (2H, m), 5.60 (1H, d, *J* 9.1Hz), 2.30 (3H, s).

Example 9

5 3-Amino-7-(4-methylphenyl)-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

Chloroacetonitrile (0.41mL, 6.4mmol) was added to a suspension of Example 8 (1.7g, 6.44mmol) in MeCN (40mL). The mixture was heated at 45 °C for 2h. Solvent was removed *in vacuo* and the residual solid was suspended in H₂O (30mL). The solid was filtered off, washed with H₂O (3 x 10mL) and Et₂O (5mL) and dried to give the title compound as an off-white solid (1.22g, 67%). δ H (DMSO-d₆) 8.01 (1H, d, *J* 9.7Hz), 7.34-7.32 (2H, m), 7.27-7.25 (2H, m), 7.00 (2H, br s), 6.45 (1H, d, *J* 9.7Hz), 2.34 (3H, s). LCMS (ES⁺) RT 3.03 minutes, 282.0 (M+H)⁺

15 Example 10

3-Bromo-6-oxo-7-phenyl-6,7-dihydro-thieno[2,3-*b*]pyridine-2-carbonitrile

To a mixture of anhydrous copper (II) bromide (23.4g) and t-butylnitrite (14.8 mL) in MeCN (600 mL) at room temperature, was added Example-3 (20g) portion wise, at such a rate to keep the internal temperature below 25°C. The addition took approximately 1 hour. Analysis by HPLC indicated almost complete conversion of starting material after a further 30 minutes of stirring. The reaction mixture was then poured onto 500mL of 1M HCl (nb caution, brown fumes given off). This was then extracted with DCM (2 x 400mL). The combined organics extracts were then washed with 1M HCl (3 x 300mL), dried over MgSO₄ and evaporated to dryness. The resulting crude product was then recrystallised from MIBK (700mL). The product was dried under vacuum at 50° to constant weight to give the title compound as a light brown solid (15.14g). δ H (CDCl₃) 7.75 (1H, d, *J* 8.5Hz), 7.55-7.70 (3H, m), 7.35 (2H, m), 6.80 (1H, d, *J* 8.5Hz). LCMS (ES⁺) RT 3.54 minutes, no parent ion observed.

30 Example 11

6-Oxo-7-phenyl-3-phenylamino-6,7-dihydro-thieno[2,3-*b*]pyridine-2-carbonitrile

Method A

To a dry 100ml 3 necked round bottomed flask, fitted with nitrogen inlet/outlet was added K_3PO_4 (5.90g), $tBu_3PH.BF_4$ (110mg), Example 3 (5.0g) and $Pd_2(dba)_3$ (85.5mg). To this mixture was added 50ml of anhydrous DME, which had been thoroughly degassed. The reaction mixture was then put through a vacuum and nitrogen cycle. To the reaction mixture was added bromobenzene (3.25g) via syringe. The reaction was then set to reflux. After 5 hours at reflux the reaction had gone to completion. The reaction mixture was cooled to ambient, held at this temperature for 1 hour. The solid was then collected by filtration. This crude solid was then slurried in 50ml of 1.0N HCl for 1 hour. The beige coloured solid, was collected by filtration washing with H_2O (50ml). The product was then dried under vacuum at $50^\circ C$, to give the title compound as a light brown solid (5.27g). δH (DMSO- d_6) 9.60 (1H, s), 8.25 (1H, d, \underline{J} 8.5Hz), 7.75-7.90 (5H, m), 7.50 (2H, m), 7.40 (2H, m), 7.30 (1H, t, \underline{J} 7.5Hz), 6.85 (1H, d, \underline{J} 8.5Hz). LCMS (ES⁺) RT 3.58 minutes, 344 (M+H)⁺

Method B

To a dry 50ml 2 necked round bottomed flask, fitted with nitrogen inlet/outlet was added Cs_2CO_3 (1.38g), (+/-)-BINAP (188mg), Example 10 (1.00g) and $Pd_2(dba)_3$ (138.4mg). To this mixture was added 20ml of anhydrous toluene, which had been thoroughly degassed. The reaction mixture was then put through a vacuum and nitrogen cycle. To the reaction mixture was added aniline (0.338g) via syringe. The reaction was then set to reflux. After 16 hours at reflux the reaction had gone to completion. The reaction mixture was cooled to ambient, held at this temperature for 1 hour. The solid was then collected by filtration. This crude solid was then slurried in 10ml of 1.0N HCl for 1 hour. The beige coloured solid was collected by filtration, washing with H_2O (10ml). The product was then dried under vacuum at $50^\circ C$, to give the title compound as a light brown solid (0.68g). δH (DMSO- d_6) 9.60 (1H, s), 8.25 (1H, d, \underline{J} 8.5Hz), 7.75-7.90 (5H, m), 7.50 (2H, m), 7.40 (2H, m), 7.30 (1H, t, \underline{J} 7.5Hz), 6.85 (1H, d, \underline{J} 8.5Hz). LCMS (ES⁺) RT 3.58 minutes, 344 (M+H)⁺

Example 12

6-Oxo-7-phenyl-3-phenylamino-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

To a 100ml round bottomed flask, fitted with nitrogen inlet/outlet was added Example 11 (1.45g) and 13.3mL of a solution of 0.382g of NaOH in H₂O (20mL), plus absolute EtOH (30mL). The reaction was then set to reflux. After approximately 1 hour at reflux the reaction had gone to completion. The reaction mixture was cooled to ambient, and poured onto 1M HCl (100ml). This mixture was then extracted with DCM (2 x 75mL). The combined organics were washed with 1MHCl (2 x 50mL), dried (MgSO₄) and evaporated to dryness. The resulting crude product was then passed down a silica column eluting with 4:1 DCM:EtOAc. The product was then dried under vacuum at 50°C, to give the title compound as a light yellow solid (1.47g). δ H (DMSO-d₆) 8.85 (1H, s), 7.60-7.40 (5H, m), 7.30-7.10 (5H, m), 6.80 (3H, m), 6.30 (1H, d, *J* 8.5Hz). LCMS (ES⁺) RT 2.92 minutes, 362 (M+H)⁺.

Example 13

3-Bromo-7-(2-chlorophenyl)-6-oxo-6,7-dihydrothieno[2,3-b]pyridine-2-carbonitrile

Example 5 (1.17g, 3.88mmol) was suspended in MeCN (20mL). Copper (II) bromide (953mg, 4.27mmol) was added followed by t-butyl nitrite (0.64mL, 5.43mmol). The mixture was stirred at r.t. for 3h then partitioned between 2M HCl aq (100mL) and EtOAc (100mL). The organic layer was washed with 2M HCl aq (50mL), 2M NaOH aq (50mL) and water (25mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (silica, 0 to 5% EtOAc in DCM) gave the title compound as a pale brown solid (980mg, 67%). δ H (CDCl₃) 7.70 (1H, d, *J* 9.7Hz), 7.61 (1H, dd, *J* 1.7, 7.7Hz), 7.52-7.44 (2H, m), 7.34 (1H, dd, *J* 1.7, 7.7Hz), 6.70 (1H, d, *J* 9.7Hz). LCMS (ES⁺) RT 3.56 minutes, 365 (M+H)⁺.

Example 14

7-(2-Chlorophenyl)-3-[(4-fluoro-3-methylphenyl)amino]-6-oxo-6,7-dihydrothieno[2,3-b]pyridine-2-carbonitrile

A mixture of Example 13 (500mg, 1.37mmol), 4-fluoro-3-methyl aniline (206mg, 1.64mmol), Cs₂CO₃ (625mg, 1.92mmol), BINAP (85mg, 0.37mmol, 10mol%) and Pd₂(dba)₃ (63mg, 0.0685mmol, 5mol%) in toluene was heated at reflux for 18h. A second charge of BINAP (42mg, 5mol%) and tris(dibenzylideneacetone)-dipalladium(0) (31.5mg, 2.5mol%) was added and

the mixture heated at reflux for a further 4 days. The mixture was partitioned between DCM (100mL) and H₂O (50mL). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (silica, 10% EtOAc in DCM) gave the title compound as an off-white solid (160mg, 28%). δ H (DMSO-d₆) 9.39 (1H, s), 8.17 (1H, d, *J* 9.7Hz), 7.87 (1H, dd, *J* 1.7, 7.9Hz), 7.79 (1H, dd, *J* 2.1, 7.7Hz), 7.75-7.66 (2H, m), 7.24-7.12 (3H, m), 6.71 (1H, d, *J* 9.7Hz), 2.29 (3H, d, *J* 1.7Hz). LCMS (ES⁺) RT 3.63 minutes, 410 (M+H)⁺

Example 15

7-(2-Chlorophenyl)-3-[(4-fluoro-3-methylphenyl)amino]-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

Sodium hydroxide (0.68mL of a 0.25M aq. solution, 0.17mmol) was added to Example 14 (136mg, 0.33mmol) in ethanol (6mL) and the mixture heated at reflux for 1h. The mixture was concentrated *in vacuo*, the residue suspended in water and the solid filtered off and dried. Purification by column chromatography (silica, 20% EtOAc in DCM) gave the title compound as a pale yellow solid (65mg, 46%). δ H (CDCl₃) 9.08 (1H, br s), 7.60-7.57 (1H, m), 7.48-7.41 (2H, m), 7.38-7.35 (1H, m), 7.06 (1H, d, *J* 9.8Hz), 6.93-6.85 (3H, m), 6.29 (1H, d, *J* 9.8Hz), 5.18 (2H, br s), 2.20 (3H, d, *J* 1.4Hz). LCMS (ES⁺) RT 3.28 minutes, 428 (M+H)⁺

Example 16

3-Amino-7-phenyl-2-(pyrrolidine-1-carbonyl)-7H-thieno[2,3-*b*]pyridin-6-one

A mixture of Example 1 (0.5g) and Intermediate 2 (0.35g) in MeCN (10 mL) was heated at reflux for 1.5h. H₂O (2.5mL) was added and the resulting mixture was concentrated *in vacuo*. The resulting solid precipitate was recovered by filtration and dried under vacuum to give 6-oxo-2-(2-oxo-2-pyrrolidin-1-yl-ethylsulfanyl)-1-phenyl-1,6-dihydro-pyridine-3-carbonitrile (0.56g). δ H (DMSO-d₆) 7.998 (1H, d, *J* 9.5Hz), 7.75 (3H, m), 7.55 (2H, m), 6.85 (1H, d, *J* 9.5Hz), 3.86 (2H, s), 3.62-3.37 (4H, m), 2.15-1.90 (4H, m). A mixture of this material (0.38g) and K₂CO₃ (0.31g) in EtOH (7.5mL) was heated at reflux for 2.5h. H₂O (10mL) was added and the mixture was concentrated under vacuum. The resulting solid product was filtered, washed

with water and dried *in vacuo* to give the title compound as an off-white solid (0.37g). δ H (DMSO- d_6) 8.12 (1H, d, J 9.4Hz), 7.66-7.50 (3H, m), 7.44 (2H, m), 7.25 (2H, br s), 6.50 (1H, d, J 9.4Hz), 3.36 (4H, m), 1.75 (4H, m). LCMS (ES⁺) RT 2.84 minutes, 340 (M+H)⁺.

5 **Example 17**

7-Phenyl-3-phenylamino-2-(pyrrolidine-1-carbonyl)-7H-thieno[2,3-b]pyridin-6-one

To a dry 50ml 3 necked round bottomed flask, fitted with nitrogen inlet/outlet was added K₃PO₄ (94mg), tBu₃PH.BF₄ (8.6mg), Example 16 (100mg) and
10 Pd₂(dba)₃ (13.5mg). To this mixture was added 10ml of anhydrous DME, which had been thoroughly degassed. The reaction mixture was then put through a vacuum and nitrogen cycle. To the reaction mixture was added bromobenzene (70mg) via syringe. The reaction was then set to reflux. After 5
15 hours at reflux the reaction had gone to completion. The reaction mixture was cooled to ambient, held at this temperature for 1 hour. The reaction mixture was then poured onto HCl (20ml, 1.0N) and extracted with DCM (2 x 50ml). The combined organics were then washed with water (50ml). The organic layer was then dried (MgSO₄) and evaporated to give the crude product
20 quantitatively as a pale yellow solid. Recrystallisation from MeOH, and drying under vacuum at 50°C, gave the title compound as an off white solid (50mg). δ H (CDCl₃) 9.61 (1H, s), 7.70-7.50 (3H, m), 7.45 (2H, m), 7.36 (1H, m), 7.30 (2H, m), 7.05 (3H, m), 6.41 (1H, d, J 9.7Hz), 3.55-3.65 (4H, m), 1.85-1.95 (4H, m). LCMS (ES⁺) RT 3.55 minutes, 416 (M+H)⁺

Example 18

25 **Sodium 3-cyano-1-cyclopropyl-6-oxo-1,6-dihydropyridine-2-thiolate**

A solution of NaHMDS (122mL of a 1.0M solution in THF, 122mmol) was added to a solution of cyclopropyl isothiocyanate (4.85g, 48.9mmol) and MeCN (25.5mL, 10eq) in THF (50mL) at -78 °C. The mixture was allowed to warm to r.t. over 2h. N,N-Dimethyluracil (5.9g, 49mmol) and EtOH (60mL)
30 were added and the mixture heated at reflux for 3h then stirred at r.t. overnight. Volatiles were removed *in vacuo*. The residue was taken up in a mixture of EtOH and EtOAc then Et₂O was added. The sticky solid was

filtered off and dried to give the title compound (11g, crude) which was used in the next step without further purification.

Example 19

3-Amino-7-cyclopropyl-6-oxo-6,7-dihydrothieno[2,3-b]pyridine-2-carbonitrile

A mixture of crude example 18 (9g, assume 42mmol) and chloroacetonitrile (2.7mL, 42mmol) in MeCN (100mL) was heated at reflux for 3h. Volatiles were removed *in vacuo*. H₂O (100mL) was added to the residue and the solid obtained filtered off and dried. The crude material was partitioned between H₂O and EtOAc and the aqueous phase extracted with EtOAc. The combined organic phases were concentrated *in vacuo*. The residue was dissolved in EtOH and the solution treated with Et₂O to give a solid which was filtered off and dried to give the title compound as a light brown solid (2.5g). δ H (CDCl₃) 7.42 (1H, d, *J* 9.6Hz), 6.52 (1H, d, *J* 9.6Hz), 4.6 (2H, br s), 3.08-3.00 (1H, m), 1.2-1.1 (2H, m), 1.08-1.0 (2H, m). LCMS (ES⁺) RT 2.532 minutes, 232 (M+H)⁺

Example 20

3-Bromo-7-cyclopropyl-6-oxo-6,7-dihydrothieno[2,3-b]pyridine-2-carbonitrile

Copper (II) bromide (0.53g, 2.37mmol) and t-butyl nitrite (0.40mL, 3.02mmol) were added to a solution of Example 19 (0.5g, 2.16mmol) in MeCN (15mL). The reaction mixture was stirred at r.t. for 4h. DCM (100mL) was added and the mixture washed with 2M HCl aq and 2M NaOH aq, dried (MgSO₄) and concentrated *in vacuo* to give the title compound (400mg, 63%). δ H (CDCl₃) 7.62 (1H, d, *J* 10.2Hz), 6.63 (1H, d, *J* 10.3Hz), 3.1-3.0 (1H, m), 1.3-1.2 (2H, m), 1.1-1.0 (2H, m). LCMS (ES⁺) RT 3.184 minutes, 296.8 (M+H)⁺

Example 21

7-Cyclopropyl-3-[(3-methylphenyl)amino]-6-oxo-6,7-dihydrothieno[2,3-b]pyridine-2-carbonitrile

Prepared from Example 20 and m-toluidine by the method of Example 14. Light yellow solid. δ H (CDCl₃) 7.25 (1H, d, *J* 9.6Hz), 7.20-7.16 (1H, m), 6.04 (1H, d, *J* 7.6Hz), 7.82-7.80 (2H, m), 6.67 (1H, s), 6.33 (1H, d, *J* 9.6Hz), 3.07-3.02 (1H, m), 2.31 (3H, s), 1.32-1.17 (2H, m), 1.14-1.07 (2H, m). LCMS (ES⁺) RT 3.336 minutes, 321.9 (M+H)⁺

Example 22**7-Cyclopropyl-3-[(3-methylphenyl)amino]-6-oxo-6,7-dihydrothieno[2,3-b]pyridine-2-carboxamide**

Prepared from Example 21 by the method of Example 15. Light yellow solid.

5 δ H (CDCl₃) 8.65 (1H, br s), 7.25-7.11 (2H, m), 6.88 (1H, d, *J* 7.5Hz), 6.83-6.80 (2H, m), 6.24 (1H, d, *J* 9.7Hz), 5.68 (2H, br s), 3.08-3.05 (1H, m), 2.3 (3H, s), 1.34-1.23 (2H, m), 1.15-1.13 (2H, m). LCMS (ES⁺) RT 2.888 minutes, 340 (M+H)⁺

Example 23

10 **6-Oxo-7-phenyl-3-*m*-tolylamino-6,7-dihydrothieno[2,3-b]pyridine-2-carbonitrile**

Method A

To a dry 2L jacketed vessel, fitted with nitrogen inlet/outlet was added K₃PO₄ (120g), 3-bromotoluene (69.7g) and Example 3 (100.5g). To this mixture was
 15 added 1L of anhydrous DME. The reaction mixture was then thoroughly degassed by purging with nitrogen vigorously for approximately 1 hour. To the reaction mixture was then added tBu₃PBF₄ (6.57g) and Pd₂(dba)₃ (2.59g) washing in with DME (50ml). The reaction was then set to reflux. After ~3
 20 hours at reflux the reaction had gone to completion. The reaction mixture was cooled to ambient, and then poured onto 1L of 0.1M EDTA solution. The resulting granular solid was then stirred at RT for 1 hour. The solid was then collected, by filtration washing with water (3 x 200ml). The product was then dried under vacuum at 50°C, to give the title compound as a beige solid (122g, 92.0%). HPLC, indicated PAR of 92.5%, and 5.0% of the bis-arylated
 25 product. This could be further purified by recrystallisation from acetic acid to give the title compound. δ H (DMSO-d₆) 7.60-7.70 (3H m), 7.40 (2H m), 7.35 (1H, d, *J* = 9.7Hz), 7.25 (1H, m), 6.85-7.00 (3H, m), 6.50 (1H d, *J* = 9.7Hz), 6.40 (1H, s), 2.35ppm (3H, s). LCMS (ES⁺) RT 3.85 minutes, 358.2 (M+H)⁺.

Method B

30 To a dry 25ml flask was charged K₃PO₄ (1.69g), copper (I) iodide (0.08g), ethylene glycol (0.50g), 3-iodotoluene (1.75g) and Example 3 (1.07g). To this was added previously degassed anhydrous 1,4 dioxan and this mixture subjected to a vacuum/nitrogen cycle. The reaction was heated to reflux under

a nitrogen atmosphere and monitored by LC. After 1.5 hours complete conversion was achieved. The reaction was then poured into water (30ml) and extracted with DCM (30ml). The DCM was washed with 2x30ml 5% EDTA solution, the aqueous layers combined and extracted with 20ml DCM. All the organics were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was slurried in 10ml MeOH at room temperature for 2 hours, filtered, washed with MeOH (3x2ml) and dried *in vacuo* to yield the title compound (0.74g). δ H (DMSO-d₆) 7.60-7.70 (3H m), 7.40 (2H m), 7.35 (1H, d, J = 9.7Hz), 7.25 (1H, m), 6.85-7.00 (3H, m), 6.50 (1H d, J = 9.7Hz), 6.40 (1H, s), 2.35ppm (3H, s). LCMS (ES⁺) RT 3.85 minutes, 358.2 (M+H)⁺.

Method C

The compound of Example 3 (5.00 g), 3-iodotoluene (4.85 ml), copper(I) iodide (0.36 g), K₃PO₄ (7.90 g), and *N,N*-dimethylethanolamine (50 ml) were placed in a pre-dried 250 ml round-bottom flask fitted with a reflux condenser. The flask was sealed, then evacuated and back-filled with nitrogen three times. The white/pink suspension was stirred by the action of a magnetic stirring bar and heated to 80°C. The reaction developed into a brown suspension and then on to a brown solution. After 1.5 hours at this temperature the reaction was shown to be complete by hplc. The reaction was cooled to room temperature, quenched by the addition of 100 ml of water, and stirred for a further 1 h at room temperature. Filtration of the resultant suspension, washing with a further 100 ml of water, gave, after drying, a crude green/brown solid (6.78 g). The crude product (6.00 g) was recrystallised from 4 volumes of AcOH, washed with EtOAc (50 ml) and then dried under vacuum to give the title compound as a yellow solid (4.16 g). δ H (DMSO-d₆) 7.60-7.70 (3H m), 7.40 (2H m), 7.35 (1H, d, J = 9.7Hz), 7.25 (1H, m), 6.85-7.00 (3H, m), 6.50 (1H d, J = 9.7Hz), 6.40 (1H, s), 2.35ppm (3H, s). LCMS (ES⁺) RT 3.85 minutes, 358 (M+H)⁺.

Example 24

6-Oxo-7-phenyl-3-*m*-tolylamino-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

A solution of KOH (12.69g, 85+%) in water (230ml) was added to a suspension of Example 23(114g) in EtOH (345 ml). The resulting mixture was heated at reflux for 70 minutes, by which time the reaction had gone to completion. It was cooled and water (285ml) added. The suspension was filtered and washed with water (200ml). The product was dried under vacuum to give the title compound as a yellow solid (120g). δ H (CDCl₃) 8.90 (1H, s), 7.55-7.65 (3H, m), 7.4 (2H, m), 7.20-7.30 (2H, m), 6.9 (3H, m), 6.35 (1H, d, \underline{J} 9 Hz), 5.4 (2H, br s), 3.7 (2H, q, EtOH), 2.35 (3H, s), 1.25 (3H, t, EtOH). LCMS (ES⁺) RT 3.1 minutes, 376 (M+H)⁺

10 Example 25

3-Amino-7-phenyl-2-[(R)-3-(tetrahydropyran-2-yloxy)pyrrolidine-1-carbonyl]-7H-thieno[2,3-b]pyridin-6-one

A suspension of Intermediate 4 (11.6 g), Example 1 (11.75g at 100%), and K₂CO₃ (6.5 g) in acetonitrile (135 ml) was heated to reflux for 2 h. The reaction was then cooled to ambient temperature, and water (270 ml) was added. The mixture was stirred for 45 minutes, then filtered. The light brown solid was washed with water, then dried in a vacuum oven at 40 °C. The title compound was obtained in a 73 % yield (15.1 g). δ H (CDCl₃) 7.75 (1H, d, \underline{J} 9.4 Hz), 7.50-7.75 (3H, m), 7.30-7.45 (2H, m), 6.65 (1H, d, \underline{J} 9.4 Hz), 6.25 (2H, br s), 4.60-4.70 (1H, m), 4.35- 4.45 (1H, m), 3.40-3.90 (6H, m), 1.40-2.20 (8H, m). LCMS (ES⁺) RT 3.36 min, 440 (M+H)⁺.

20 Example 26

3-(4-Fluoro-3-methylphenylamino)-7-phenyl-2-[(R)-3-(tetrahydropyran-2-yloxy)pyrrolidine-1-carbonyl]-7H-thieno[2,3-b]pyridin-6-one

25 Method A

To a dry 100 ml 2 necked round bottomed flask, fitted with nitrogen inlet/outlet was added Example 25 (1 g), K₃PO₄ (0.72 g), P^tBu₃H.BF₄ (0.072 g) and Pd₂(dba)₃ (0.105 g). To this mixture was added 5-bromo-2-fluorotoluene (0.517 g) as a solution in anhydrous DME (30 ml). This solution had been thoroughly degassed. The reaction mixture was then put through a vacuum and nitrogen cycle. The reaction was then set to reflux. After 21 hours at reflux the reaction had gone to approximately 98 % completion. The reaction mixture was cooled to ambient, and then poured onto EDTA solution (30 ml, 5%),

before filtering through celite. This was then extracted with DCM (2 x 30ml). The combined organics were then washed with water (50 ml), dried over MgSO₄ and evaporated to give a brown oil. This was then crystallised by stirring in 3 volumes of EtOH, then dried under vacuum at 40°C, to give the

5 title compound as a pale yellow solid (0.70 g). δ H (DMSO-d₆) 8.90 (1H, d, *J* 15Hz), 7.67-7.50 (6H, m), 7.02-6.97 (1H, m), 6.85-6.84 (1H, m), 6.77-6.72 (1H, m), 6.49 (1H, d, *J* 9.5), 4.61-4.48 (1H, m), 4.19-4.15 (1H, m), 3.71-3.24 (6H, m), 2.16 (3H, s), 1.79-1.27 (8H, m). LCMS (ES⁺) RT 4.02 minutes, 549 (M+H)⁺

10 Method B

To a dry 100 ml 3 necked round bottomed flask, fitted with nitrogen inlet/outlet was added Example 25 (0.50 g), K₃PO₄ (0.484 g) and CuI (0.024 g). To this mixture was added a thoroughly degassed solution of 5-iodo-2-fluorotoluene (0.30 g) and ethylene glycol (0.141 g) in isopropanol (20 ml). The reaction

15 mixture was then put through a vacuum and nitrogen cycle. The reaction was then set to reflux. After 26 hours at reflux the reaction had gone to approximately 85 % conversion. The reaction mixture was cooled to ambient, and then poured onto 1 M HCl solution (25 ml). This was then extracted with DCM (2 x 50 ml). The combined organics were then washed with water (50

20 ml), dried over MgSO₄ and evaporated to give a crude brown oil. Crystallisation from 3 volumes of EtOH yielded the title compound as a pale yellow solid (0.125 g). δ H (DMSO-d₆) 8.90 (1H, d, *J* 15Hz), 7.67-7.50 (6H, m), 7.02-6.97 (1H, m), 6.85-6.84 (1H, m), 6.77-6.72 (1H, m), 6.49 (1H, d, *J* 9.5Hz), 4.61-4.48 (1H, m), 4.19-4.15 (1H, m), 3.71-3.24 (6H, m), 2.16 (3H, s),

25 1.79-1.27 (8H, m). LCMS (ES⁺) RT 3.99 minutes, 549 (M+H)⁺

Example 27

3-(4-Fluoro-3-methylphenylamino)-2-((R)-3-hydroxypyrrolidine-1-carbonyl)-7-phenyl-7H-thieno[2,3-b]pyridin-6-one

A suspension of Example 26 (5.8 g) in EtOH (180 ml) was treated with 1.3 M HCl (32 ml). The mixture was stirred at ambient temperature overnight. The

30 pH was adjusted to 8 using 2 M sodium hydroxide. The resulting mixture was concentrated to remove the EtOH, and the solid was filtered off, washed with water, then reslurried in 25 ml water for 1 h. The suspension was filtered,

washed with water, and the product was dried in a vacuum oven at 45 °C overnight. The beige solid was recrystallised from 19 volumes of EtOH, to give the title compound as a crystalline solid (3.52 g). δ H (CDCl₃) 9.65 (s, 1H), 7.65-7.50 (3H, m), 7.35-7.50 (2H, m), 7.25 (1H, d, \underline{J} 9 Hz), 6.85-7.0 (3H, m), 6.40 (1H, d, \underline{J} 9 Hz), 4.5 (1H, br s), 3.55-3.80 (4H, m), 2.25 (3H, br s), 1.95-2.05 (2H, m), 1.80 (1H, d, \underline{J} 4 Hz) LCMS (ES⁺) RT 2.90 min, 464 (M+H)⁺

Example 28

3-Amino-2-((S)-2-hydroxymethyl-pyrrolidine-1-carbonyl)-7-phenyl-7H-thieno[2,3-b]pyridin-6-one

- 10 A mixture of Intermediate 5 (1.2g), Example 1 (1.69g at 100%) and K₂CO₃ (0.93g) in MeCN (10 ml), was heated at reflux for 2 hours. Water (10 ml) was added and any insoluble material was removed by filtration. The resulting filtrate was concentrated under vacuum and then extracted with DCM (3 x 5 ml). The combined organic extracts were washed with brine (5 ml), dried over sodium sulphate and then evaporated to leave the title compound as a yellow foam (1.34g). δ H (DMSO-d₆) 8.26 (1H, d, \underline{J} 9 Hz), 7.8-7.65 (3H, m), 7.63-7.5 (2H, m), 7.44-7.34 (2H, m), 6.66 (1H, d, \underline{J} 9 Hz), 4.80 (1H, br s), 4.25 (1H, m), 3.65-3.35 (4H, m), 2.1-1.8 (4H, m). LCMS (ES⁺) RT 2.44 min, 370 (M+H)⁺.

Example 29

- 20 3-(4-Fluoro-3-methylphenylamino)-2-((S)-2-hydroxymethylpyrrolidine-1-carbonyl)-7-phenyl-7H-thieno[2,3-b]pyridin-6-one.

- To a dry 25ml flask fitted with nitrogen inlet/outlet was added K₃PO₄ (0.589g), ethylene glycol (0.178g), 2-fluoro-5-iodotoluene (0.368g), copper (I) iodide (0.028g) and Example 28 (0.516g). To this was added previously degassed anhydrous propan-2-ol (10ml), this was then subjected to a nitrogen/vacuum cycle. The reaction was then heated to reflux for 17.5 hours under a nitrogen atmosphere. After this time the reaction was filtered, and the liquors poured into water (50ml). This was then extracted with DCM (1x30ml and 2x20ml), the organic layers combined and washed with 1M ammonia solution (1x100ml) then 1M ammonia solution (1x50ml) and water (1x50ml). The organics were dried over sodium sulfate and concentrated to dryness under reduced pressure. The residue was then columned over silica (30g) using DCM/EtOAc as eluent. This afforded 0.140g of the title compound. δ H

(DMSO-d₆) 8.74 (1H, s), 7.78-7.75 (1H, d, J=9.7Hz), 7.65-7.61 (3H, m), 7.58-7.51 (2H, m), 7.02-6.96 (1H, t), 6.82-6.79 (1H, m), 6.76-6.72 (1H, m), 6.53-6.49 (1H, d, J=9.7Hz), 4.63-4.60 (1H, t), 3.89 (1H, broad), 3.28-3.21 (3H, m), 2.80-2.78 (1H, m), 2.14 (3H, s), 1.71-1.51 (4H, m). LCMS ES⁺ RT 3.29min, 478.0 (M+H)⁺.

Example 30

3-Bromo-6-oxo-7-phenyl-6,7-dihydro-thieno[2,3-b]pyridine-2-carboxylic acid ethyl ester

t-Butylnitrite (90% technical grade, 10 ml) and copper (II) bromide (16.66 g) were stirred in MeCN (200 ml) in a 1 ltr. jacketed vessel at 10°C under nitrogen. To this cooled mixture was added Example 4 (20 g) in ~ 1 g portions over 90 min. After a further hour at 10°C the reaction was allowed to warm to room temperature. The reaction mixture was poured onto 300 ml of 1 M HCl and stirred for 30 min. (CAUTION: brown fumes). The resultant green suspension was filtered to give a crude orange solid which was washed with water (2 x 200ml). Recrystallisation of the crude solid from 7 volumes of MIBK gave the title compound as a yellow/orange solid (17.81 g). δ H (DMSO-d₆) 7.90 (1H, d, J 10), 7.50-7.70 (5H, m), 6.90 (1H, d, J 10), 4.25 (2H, q, J 7), 1.25 (3H, t, J 7); LCMS (ES⁺) RT 3.78 minutes, (M)⁺ 378.

Example 31

3-Amino-2-nitro-7-phenyl-7H-thieno[2,3-b]pyridine-6-one

To 36.6g of Example 1 was added 400ml of acetonitrile. The resulting suspension was heated to 70°C and 22.5g bromonitromethane was added dropwise over 20 minutes. The reaction was heated at reflux for a further 100 minutes before cooling in an ice bath. The resultant precipitate was isolated by suction and washed well with water. After drying under vacuum at 55°C, a yield of 35.9g of the title compound was obtained. δ H (DMSO-d₆) 6.60 (1H, d, J=9.4Hz), 7.50 (2H, m), 7.62 (3H, m), 8.25 (1H, d, J=9.4). LCMS (ES⁺) RT 2.64 minutes, 288 (M+H)⁺.

Example 32

3-Bromo-2-nitro-7-phenyl-7H-thieno[2,3-b]pyridine-6-one

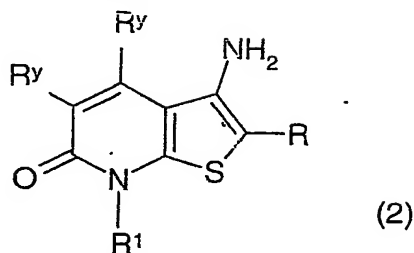
To a 500ml flask was added 350ml of acetonitrile. With stirring under a nitrogen atmosphere was added t-butylnitrite (15.1g) and copper (II) bromide

(29.9g). The resulting mixture was cooled to 6°C and Example 31 (35g) was added in portions over 4 hours, while maintaining the temperature below 10°C. The reaction was then allowed to warm to ambient temperature and stirred for 16hours. The reaction mixture was poured into 280ml of 2M hydrochloric acid and the product obtained by suction, washing with water. After drying, the crude product was purified by silica gel chromatography to give the title compound as a yellow powder (24.6g). δ H (DMSO-d₆) 6.80 (1H, d, J=9.4Hz), 7.59 (2H, m), 7.68 (3H, m), 7.98 (1H, d, J=9.4). LCMS (ES⁺) RT 3.54 minutes, 351 (M+H)⁺.

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CLAIMS

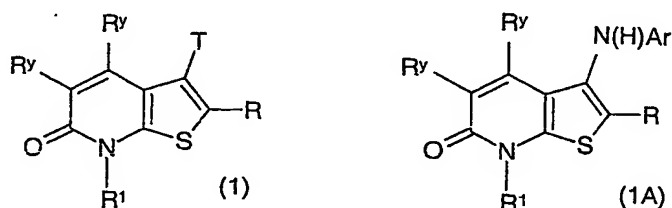
1. A compound of formula (2):



- 5 wherein:
- R is a $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{Alk}^2$, $-\text{COC}_{1-6}\text{alkyl}$ or $-\text{CONHet}^2$ group;
 Alk^2 is an optionally substituted alkyl, arylalkyl-, aryl, aryloxyalkyl-, alkanoyloxyalkyl or aroyloxyalkyl- group;
 NHet^2 is an optionally substituted 4 to 6 membered heterocycloalkyl group
 10 attached through a nitrogen atom to the group $-\text{CO}$;
 R^1 is an optionally substituted aryl, heteroaryl, cycloalkyl or heterocycloalkyl group;
 R^y , which may be the same or different, is each a hydrogen atom or a hydrogen atom precursor;
 15 and the salts, solvates, hydrates, protected derivatives and N-oxides thereof.
2. A compound according to Claim 1 in which R^1 is an optionally substituted phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, thienyl, indolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or group.
- 20 3. A compound according to Claim 2 wherein R^1 is an optionally substituted phenyl or cyclopropyl group.
4. A compound according to any one of Claims 1 to 3, in which each R^y is
 25 a hydrogen atom.
5. A compound according to any one of Claims 1 to 4, in which Alk^2 is a C_{1-6} alkyl group.

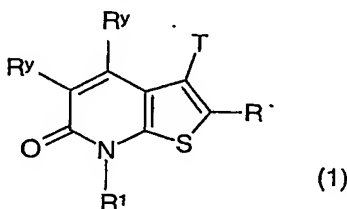
6. A compound according to any one of Claims 1 to 4, wherein R is a –CN, –CO₂CH₃, –CO₂CH₂CH₃, –COCH₃ or –CONHet² group.

7. Use of a compound of formula (2) in the manufacture of a compound of formula (1) or (1A):



wherein R, R¹ and R^y are as defined in any one of Claims 1 to 6, T is a halogen atom; and Ar is an optionally substituted aromatic or heteroaromatic group.

8. A process for the manufacture of a halide of formula (1):

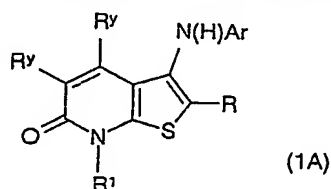


wherein R, R¹ and R^y are as defined in any one of Claims 1 to 6 and T is as defined in Claim 7;

which comprises diazotization of a compound of formula (2) as defined in any one of Claims 1 to 6, followed by halide displacement.

9. A process according to Claim 8 wherein the reaction is carried out in the presence of an alkyl nitrite or sodium nitrite in the presence of an acid, followed by addition of a copper salt, in the presence of a solvent.

10. A process for the manufacture of a compound of formula (1A):



wherein R, R¹ and R^y are as defined in any one of Claims 1 to 6 and Ar is an optionally substituted aromatic or heteroaromatic group;

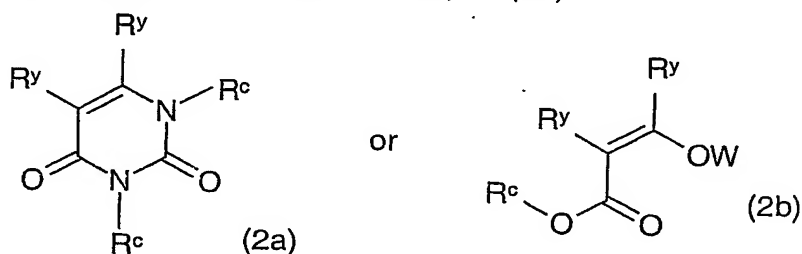
which comprises reacting a compound of formula (2), as defined in any one of Claims 1 to 6, with a compound ArQ, wherein Q is a leaving group, in the presence of a transition metal catalyst.

11. A process according to Claim 10 wherein the reaction is carried out in the presence of a solvent, using a palladium catalyst, a phosphine ligand and a base.

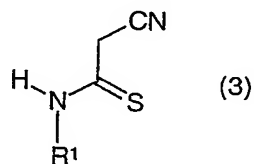
12. A process according to Claim 10 wherein the reaction is carried out in the presence of a copper catalyst.

13. A process for the manufacture of a compound of formula (2), according to any one of Claims 1 to 6, which comprises the steps of:

a) reacting a compound of formula (2a) or (2b):

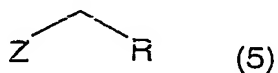


wherein R^c is an optionally substituted alkyl group, W is a hydrogen atom or metal ion or amine salt; with a compound of formula (3),



wherein R¹ is as defined herein;

b) followed by reaction with a compound of formula (5):



wherein R is as defined in Claim 1 and Z is a leaving group.

14. The process according to Claim 13 wherein W is a metal ion.
15. The process according to Claim 13 or Claim 14 wherein step a) is performed in the presence of a base.

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16. The process according to Claim 15 wherein step a) of the process is carried out in the presence of a base selected from a lithium base, a silazane, a carbonate, an alkoxide, a hydroxide, a hydride, an organic amine, or a cyclic amine.

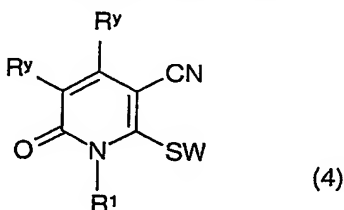
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17. The process according to any one of Claims 13 to 16 wherein the reaction is carried out in an organic solvent.

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18. The process according to Claim 17 wherein step a) and step b) is each carried out in a organic solvent, which may be the same or different in each step, selected from an amide, an ether, an alcohol or acetonitrile.

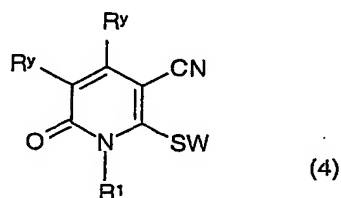
19. The process according to any one of Claim 13 to 16 wherein an intermediate of formula (4) is isolated after step a):



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wherein R¹ and R^y are as defined in any one of Claims 1 to 6 and W is as defined in Claims 13 or 14.

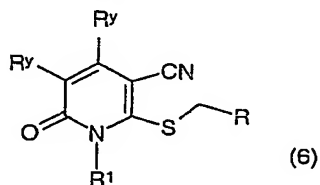
20. A compound of formula (4):



25

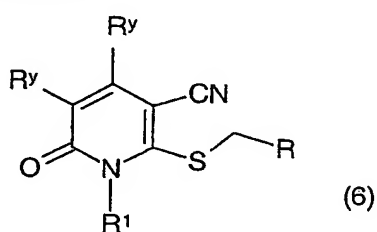
wherein R¹ and R^y are as defined in any one of Claims 1 to 6 and W is as defined in Claims 13 or 14.

21. The process according to any one of Claims 13 to 20 wherein an intermediate of formula 6 is isolated during step b):



5 wherein R¹, R and R^y are as defined in any one of Claims 1 to 6.

22. A compound of formula (6):



wherein R¹, R and R^y are as defined in any one of Claims 1 to 6.

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